Experiments in the synthesis of pyrido [1, 2-a] pyrazinium salts

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EXPERIMENTS IN THE SYNTHESIS

OF

PYRIDO [1,2-a] PYRAZINIUM SALTS

BY

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A THESIS

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SYNOPSIS

The methods of synthesis of quinolizinium and pyrazidiinium salts are briefly reviewed.

The object of the work was to establish satisfactory and if possible, general methods of synthesis of pyrido [1,2-a] pyrazinium salts and some of their oxygenated derivatives in quantities which permit a detailed study of their properties.

The method envisaged for the preparation of pyrido [1,2-a] pyrazinium salts was the cyclisation in acid media of acetaldehyde - (2- pyridylmethyleneamino) diethylacetal. The quaternary salts isolated were not pyrido [1,2-a] pyrazinium salts hence the N,N- di - (2- pyridylmethylene) pyrazidiinium cation (III) is proposed.

Hydrogenation of these quaternary salts gave compounds of molecular formula ($C_8H_{11}XN_2$) a possible structure being the N,N- di - [2- (3,4,5,6 - tetrahydropyridyl) methylene] pyrazidiinium dihalide system (LXII).

The reduction of the quaternary salts (III) with sodium borohydride in aqueous methanol gave N,N- di - (2- picolyl) perhydropyrazine.

The action of aqueous alkali on the quaternary salts (III) gave a red solid, subsequent treatment of which with ethanolic hydrohalic acids gave the N,N- di - (2- picolyl) 2,5 - dioxoperhydropyrazinium dihydrohalide.

Treatment of acetaldehyde - (methyl - 2 - pyridylmethyleneamino) diethylacetal with concentrated mineral acids gave the corresponding methyl derivatives (LXXVII) of the quaternary salts (III).

Reactions analogous to those carried out on the unsubstituted quaternary salts (III), when repeated on the methyl substituted salts (LXXVII) gave the corresponding methyl substituted derivatives.

The action of concentrated aqueous hydrobromic acid on a mixture of pyridine - 2 - aldehyde and 2 - bromoethylamine hydrobromide did not give the expected diquaternary system (LXXXIII) but gave instead a compound (LXXXIV) of molecular formula $(C_{14}H_{15}Br_2N_3O)_n$, the structure of which has not yet been established.

ACKNOWLEDGEMENTS

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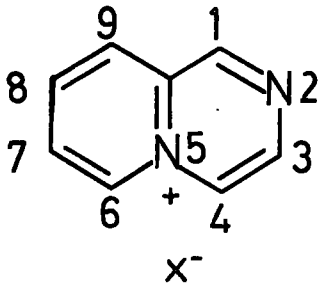
CONTENTS

INTRODUCTION

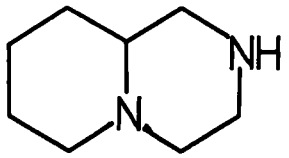
NOMENCLATURE.

The nomenclature and abreviations used in this thesis are those recommended in the Handbook for Chemical Society Authors 1960, published by the Chemical Society. The ring index system will be used throughout for naming "fused" cyclic systems, examples of which are given below.

The bicyclic fused ring system in which the 4a bridgehead and 2 carbon atoms of naphthalene have been replaced, respectively, by a quaternary and a tertiary nitrogen atom, will be designated the pyrido [1,2-a] pyrazinium ion (I). The corresponding saturated base (II) will be referred to as perhydropyrido [1,2-a] pyrazine.

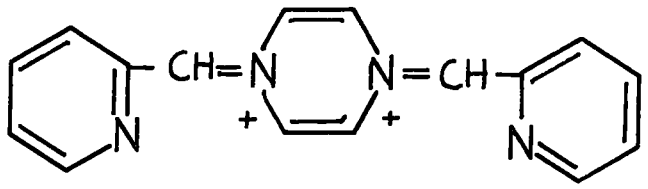


(I)



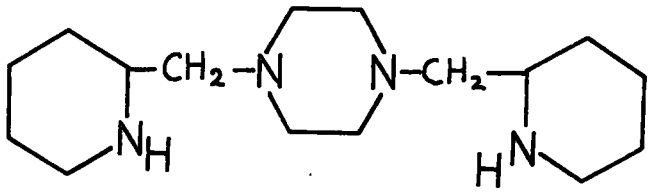
(II)

The compounds (III), (IV) and (V) will be designated N,N - di - (2-pyridylmethylene) pyrazidiinium dihalide, perhydro- N,N-di- (2- picolyl) pyrazine and pyrido [1,2-a] imidazo [3,2-c] pyrazidiinium dihalide respectively.



$2X^-$

(III)



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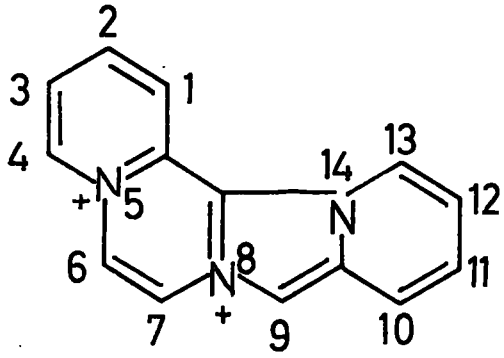


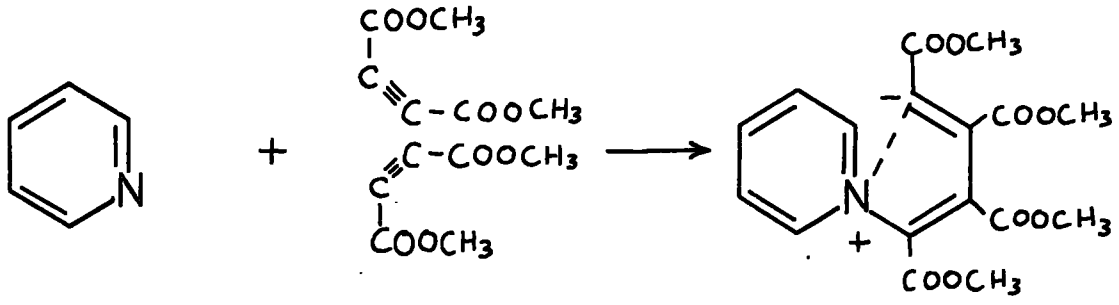
$2X^-$

(V)

HISTORICAL INTRODUCTION.

The chemistry of quinolizine and its homologues was reviewed by Thyagarajan[1] in 1954, and so contains only a few references to the fully aromatic quinolizinium cation and its derivatives. Although a cationic quinolizinium structure has long been known to occur in several polycyclic compounds[2,3], the simple quinolizinium cation was unknown until 1951. Since this review[1] was published, considerable progress has been made in the chemistry of quinolizinium salts, and consequently an account of the methods of synthesis will be given.

Diels and Alder[4] recorded that the addition of acetylene dicarboxylic acid or its esters to aromatic ring systems took place across the azomethine linkage, -C=N- , of an aromatic heterocyclic nucleus, and that similar addition products were obtained with pyridine, isoquinoline, 2- picoline, stilbazole and phenanthridine, all of which could be converted to quinolizine derivatives. The reaction between pyridine and the dimethyl ester of acetylene dicarboxylic acid in ethereal solution at room temperature gave rise to three products[5,6,7]; a "liable" red adduct (VI), a stable yellow adduct suggested to be (VII), and "Kashimoto's" compound, suggested to be (VIII).



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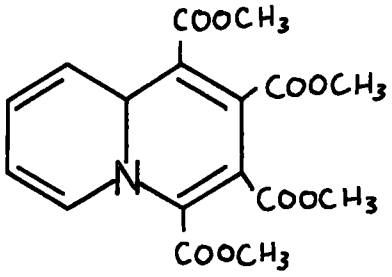
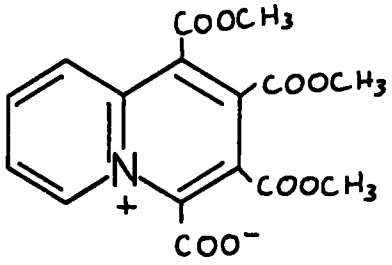
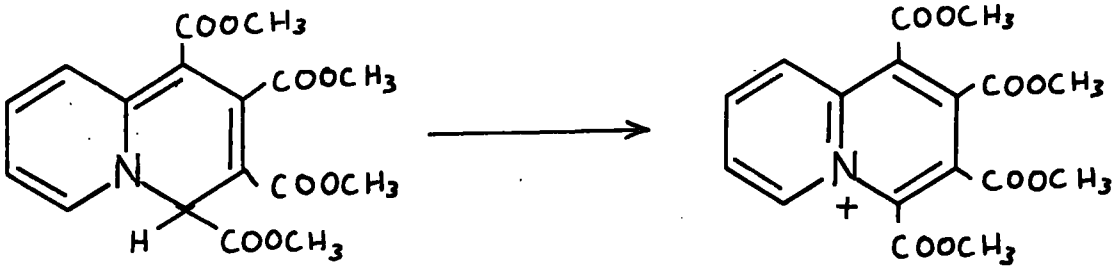


(VII)



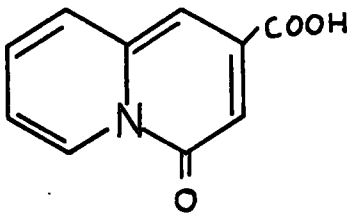
(VIII)

Diels et. al.[6] reported the synthesis of the 1,2,3,4 - tetramethoxycarbonyl compound (X) by oxidation of tetramethyl - 4 H- quinolizine-1,2,3,4 - tetracarboxylate (IX) with methanolic bromine to give the perbromide (X;X = Br_3).

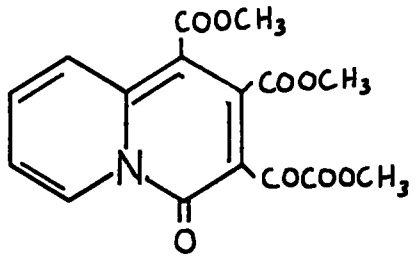


(IX) (X)

The ultraviolet spectrum of this salt closely resembled that of the simple quinolizinium cation[8,9]. The structure of the stable yellow adduct obtained by Diels and Alder[5,6,7] and suggested to be (VII), has recently been established by Acheson and Taylor[10], and Jackman, Johnson and Tebby[11] as the 4 H- isomer (IX). Woodward[12] has independantly proved, by a number of experiments, including degradation to compounds identical with synthetic 4- oxoquinolizine - 2 - carboxylic acid (XI) and its methyl ester, that "Kashimoto's" compound initially suggested to be (VIII), is in fact the lactam (XII). The infrared and ultraviolet absorption spectra of "Kashimoto's" compound resemble that of quinolizin - 4 - one[13].



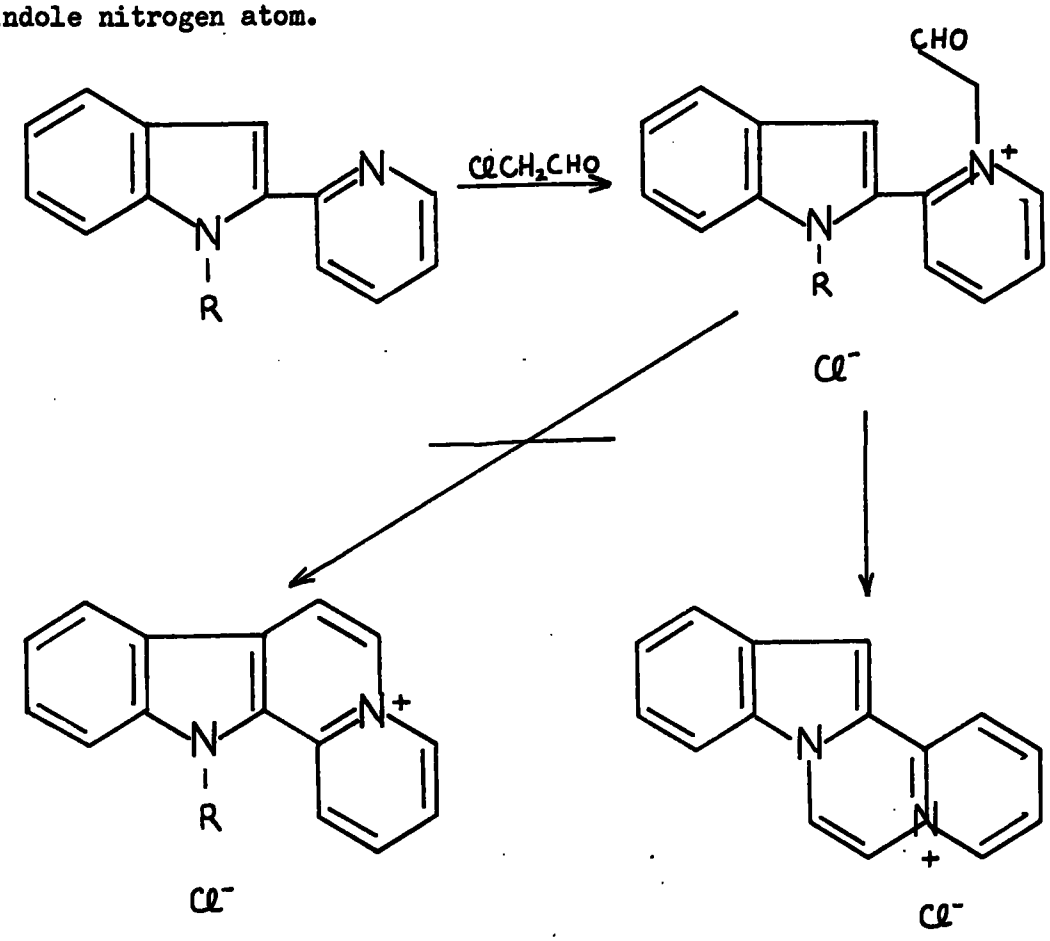
(XI)



(XII)

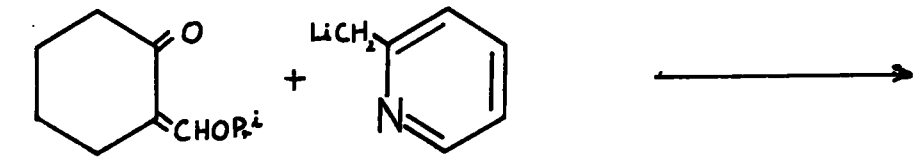
Fresh interest in the quinolizinium ion was aroused by the simultaneous discovery in 1949, by Bentley and Stevens[14] and Woodward and McLamore[3], of its presence in the alkaloid sempervirine. Bentley and Stevens[14] attempted the synthesis of the parent aromatic compound 12H - indolo [2,3-a] quinolizinium chloride (XIII; R=H). Quaternisation of 2,2' - pyridylindole with chloroacetaldehyde, followed by cyclisation with hydrochloric acid, yielded the compound (XIV) instead of the expected

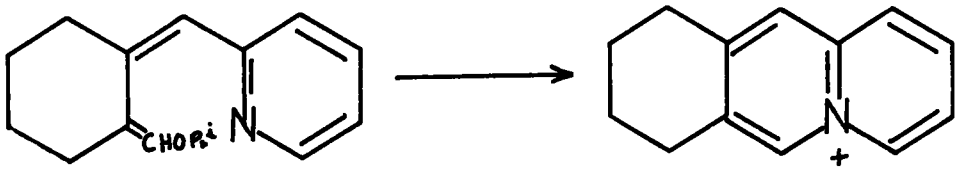
compound (XIII; R=H); cyclodehydration occuring preferentially onto the indole nitrogen atom.



(XIII) (XIV)

Additional examples of quinolizinium systems were obtained by Woodward and McLamore[3] who unambiguously synthesised a number of sempervirine metho salts. Using a model synthesis, the same authors prepared 7,8,9,10 - tetrahydrobenzo [b] quinolizinium picrate (XV; X = picrate) in 51% yield, by condensation of 2- picolyl - lithium with 2-isopropoxymethylene cyclohexanone[15] followed by cyclisation with mineral acid.

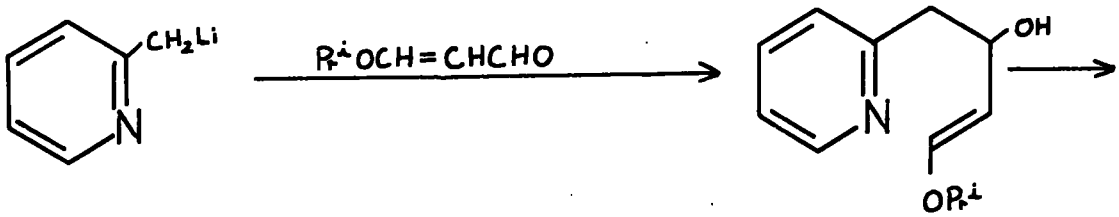


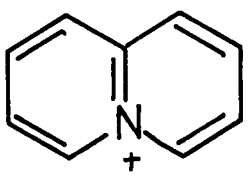


X^-

(XV)

Although Diels et.al. and other workers had earlier described more complex derivatives, the first synthesis of simple unsubstituted quinolizinium salts, in low yield, was achieved by Beaman[16] in 1951 who condensed 2- picolyl - lithium with 3- <u>iso</u>propoxyacrolein. Cyclisation and dehydration of the intermediate alcohol, with acid, gave the required quinolizinium salt (XVI).

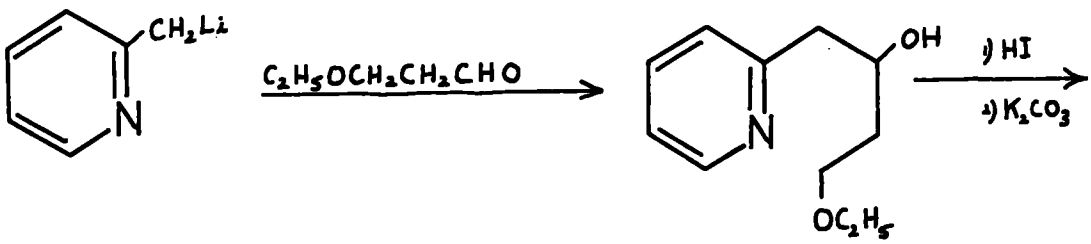




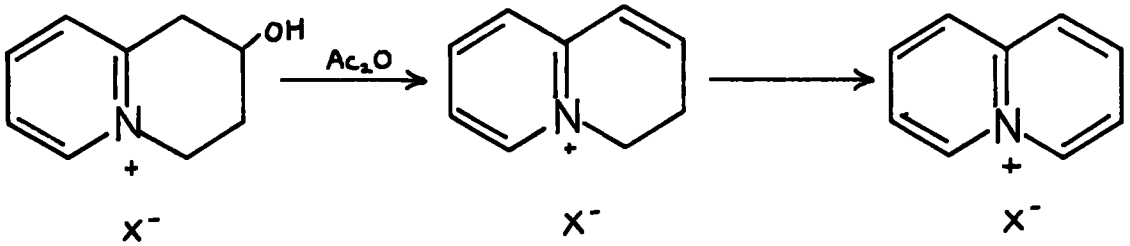
X^-

(XVI)

The 2 - ethyl - 3 - methyl homologue of (XVI) was obtained[17] similarly from ethyl - 2 - ethoxyvinyl ketone. Boekelheide and Gall[8] improved the method by replacing 3- isopropoxyacrolein with 3-ethoxypropionaldehyde and obtained the alcohol (XVII) in high yield. Treatment with hydriodic acid followed by neutralisation with alkali, readily yielded the cyclic quaternary salt (XVIII; X = I). Dehydration of this with acetic anhydride and subsequent dehydrogenation using chloranil gave the desired quinolizinium halide (XVI; X = I).



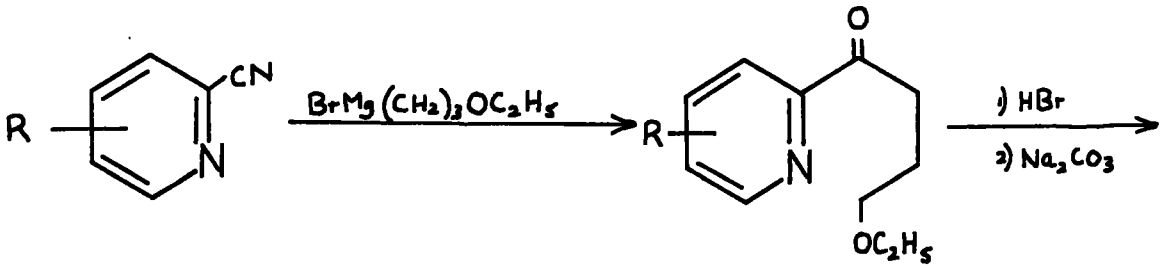
(XVII)



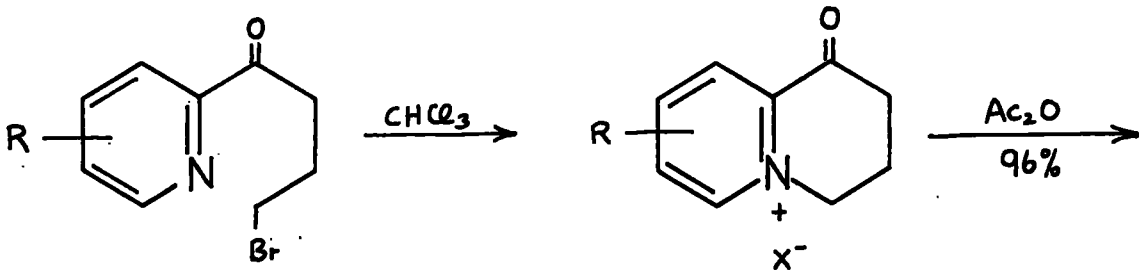
(XVIII) (XIX) (XVI)

Dehydrogenation of the dihydro compound (XIX; X = I) in butanol with palladium-charcoal catalyst gave quinolizinium iodide in 30% yield. Boekelheide and Ross[18] obtained essentially the same yields in the preparation of the 6- methyl homologue of (XVI) from 2,6- lutidine, though the yield in the dehydrogenation stage was raised to 42% by the use of a platinum catalyst in nitrobenzene as solvent. Richards and Stevens[19] modified the method of Woodward and McLamore[3] by treating the enolether or the monoacetal of a 1,3- diketone with 2- picolyl - lithium and cyclising the resulting alcohol with acid.

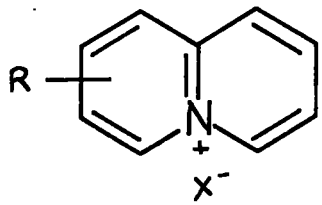
The first synthesis to produce the parent quinolizinium cation in high yield was that of Glover and Jones[20,21], who prepared quinolizinium bromide in 48% overall yield based on the starting material (2- cyanopyridine). They avoided the dehydrogenation stage by reacting 2- cyanopyridine with 3- ethoxypropylmagnesium bromide[22], and treated the resulting ketone (XX; R = H) with hydrobromic acid, followed by neutralisation of the hydrobromide with sodium carbonate. The resulting bromoketone (XXI; R = H) when boiled under reflux with chloroform cyclised to give the bromide (XXII; R = H) and subsequent dehydration with acetic anhydride gave quinolizinium bromide (XXIII; R = H, X = Br).



(XX)



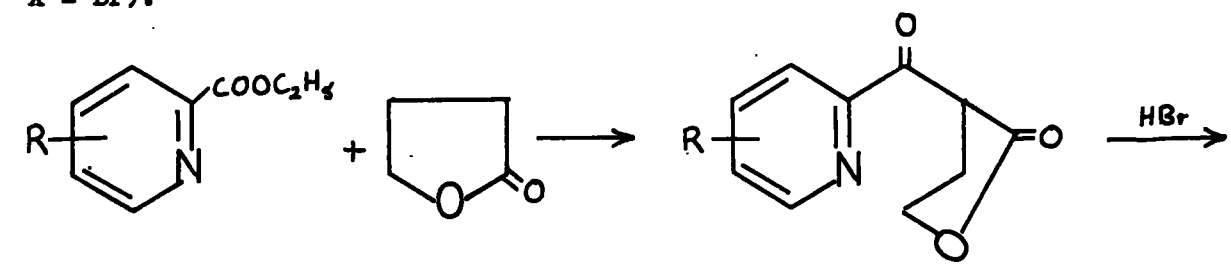
(XXI) (XXII)



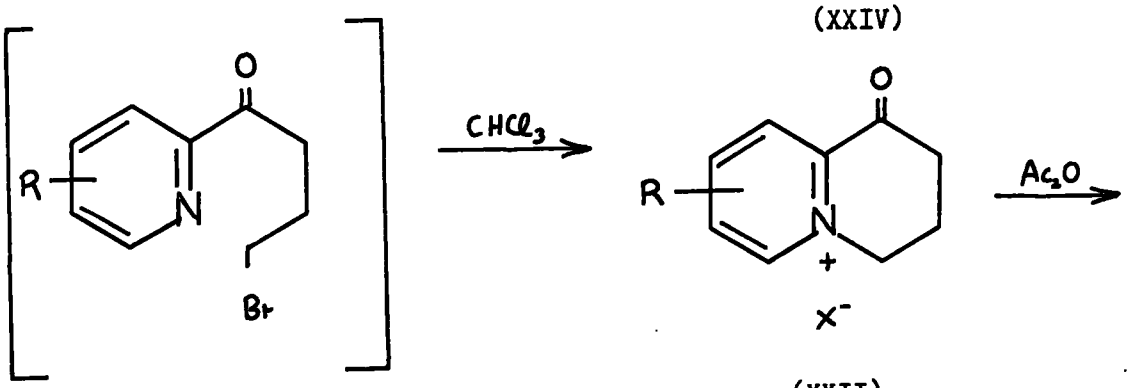
(XXIII)

The same authors extended this synthesis to the general synthesis of 2-, 3- and 4- alkyl and aryl substituted quinolizinium salts using suitably substituted precursors. Katritzky et. al.[23] also used this general method to prepare methylquinolizinium salts (XXIII; R = CH_3) using the appropriate methyl substituted 2- cyanopyridines and isolated the salts as perchlorates. Miyadera and Iwai[24] have recently reported the preparation of the parent quinolizinium bromide (XVI; X = Br) and of 1-, 2-, 3- and 4- methylquinolizinium bromides (XXIII; R = CH_3, X = Br).

Condensation of ethyl picolinate, or a suitably ring substituted methyl derivative, with 2- oxotetrahydrofuran gave the ketolactone (XXIV; R = H or CH_3), subsequent treatment with 48% hydrobromic acid afforded the bromoketone (XXI; R = H or CH_3) with concurrent decarboxylation. Cyclisation was then effected by either standing at room temperature or refluxing a chloroform solution giving the quaternary bromide (XXII; R = H or CH_3; X = Br), subsequent dehydration by boiling under reflux with acetic anhydride gave the quinolizinium bromide (XXIII, R = H or CH_3; X = Br).

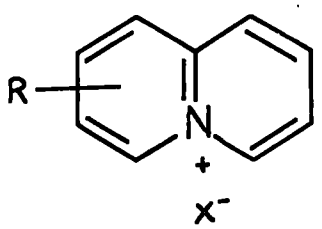


(XXIV)



(XXI)

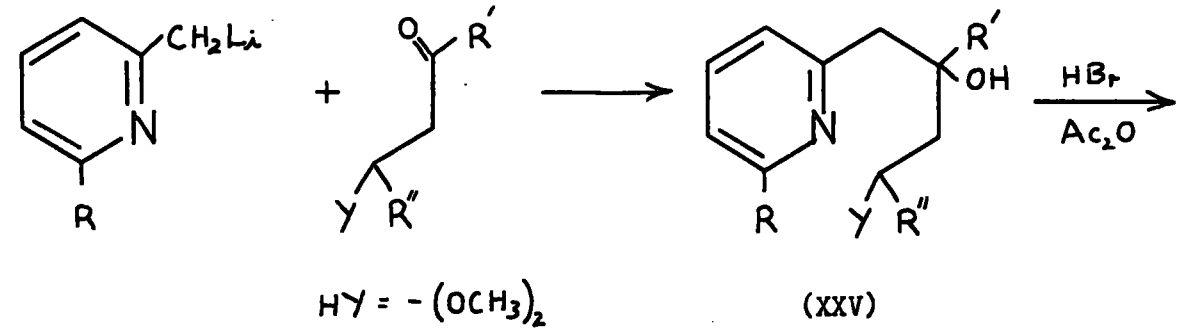
(XXII)

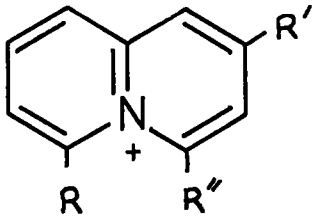


(XXIII)

The above workers also reported variations of the above prescribed method.

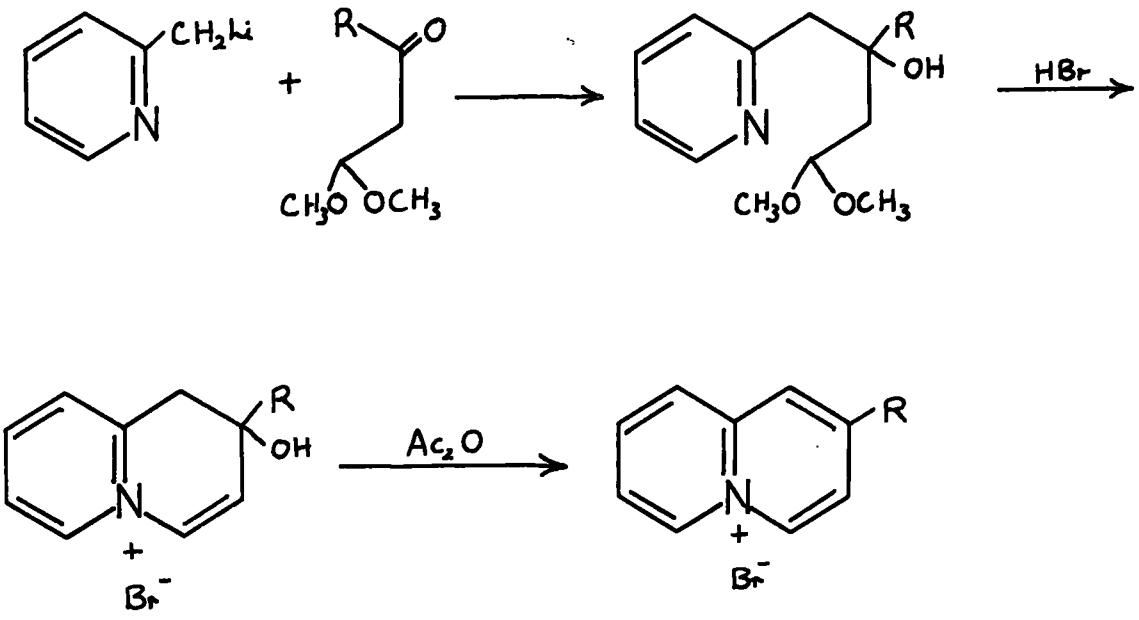
Using modifications of the synthesis described by McLamore and Woodward[3], Richards and Stevens[19] prepared the first simple 2-, 3- and 4- alkyl and aryl substituted quinolizinium salts and Hansen and Amstutz[25] prepared 2, 4, 6- trimethyl - and 2- phenyl - 4,6- dimethylquinolizinium salts by the reaction of 2, 6- lutidyl - lithium with the appropriate protected 1, 3- diketone. Cyclodehydration of the intermediate alcohol (XXV) with hydrobromic acid and acetic anhydride gave the quinolizinium salts (XXVI; R = R' = R'' = CH_3 or R' = C_6H_5, R = R'' = CH_3).





(XXVI)

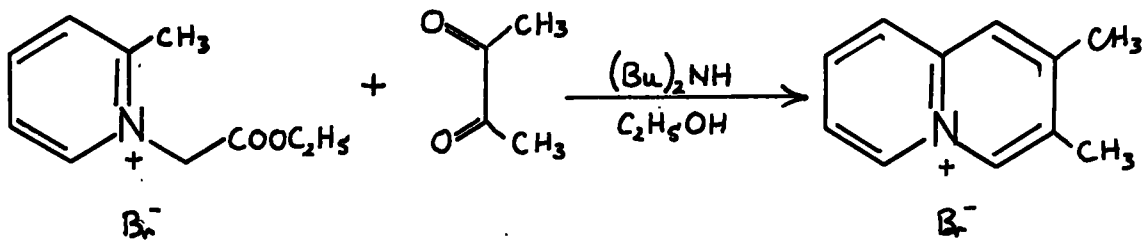
Nesmeyanov and Rybinskaya[26] have reported a synthesis, specific for the preparation of 2- substituted quinolizinium salts, which avoids the dehydrogenation stage used by Boekelheide and Gall[8] and Boekelheide and Ross[18]. They treated 2- picolyl - lithium with 2- acylacetals, cyclisation being effected by boiling under reflux with 48% hydrobromic acid. Dehydration of the resulting alcohol with acetic anhydride readily produced the quinolizinium salt (XXVII) in high yield.



(XXVII)

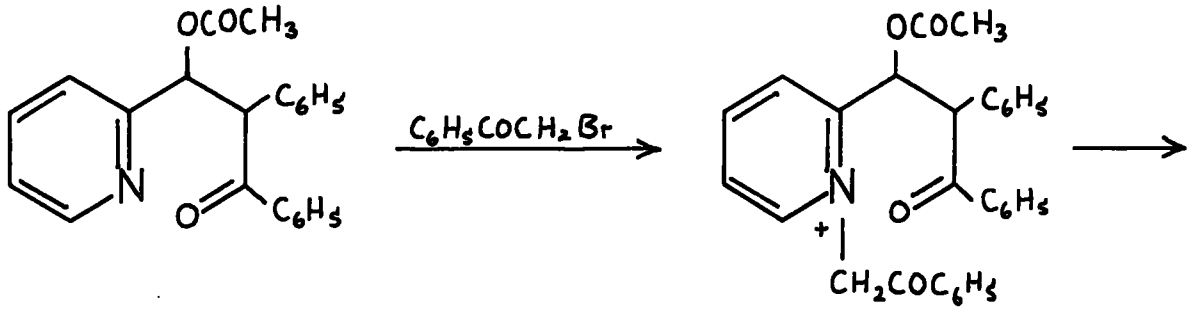
Glover and Jones[27] have reported a similar method for the synthesis of 1- alkyl and 1- aryl quinolizinium salts.

Westphal, Jann and Heffe[28] prepared 2, 3- disubstituted quinolizinium salts by condensation of suitably substituted 1, 2-diketones with an activated picolinium salt. They reacted the quaternary salt from ethylbromoacetate and 2- picoline with diacetyl, cyclodehydration being effected by heating the mixture in an ethanolic solution of dibutylamine giving 2, 3- dimethylquinolizinium bromide (XXVIII) in high yield.

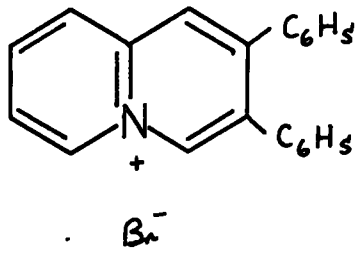


(XXVIII)

A recent British Patent[29] lists many compounds prepared by the above method. Westphal and Fiex[30] modified the above method to prepare 2, 3- diphenylquinolizinium salts. They condensed pyridine - 2 - aldehyde with phenylbenzylketone, subsequent esterification followed by quaternisation with phenacyl bromide gave the quaternary ammonium salt (XXIX). Cyclisation of the quaternary salt was effected by boiling under reflux with acetone - dibutylamine to give the 2, 3 - diphenylquinolizinium salt (XXX; X = Br).

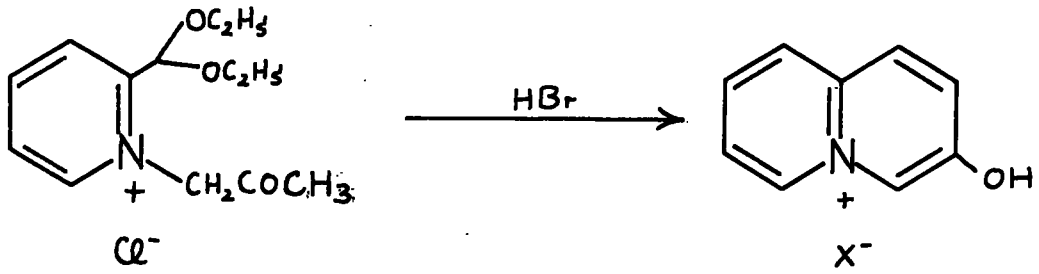


(XXIX)



(XXX)

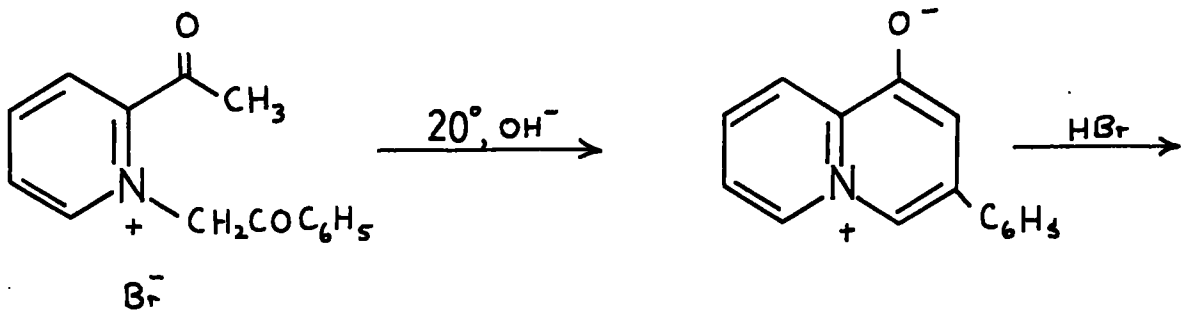
Several workers have reported the synthesis of hydroxyquinolizinium salts. Glover and Jones[31] and Fozard and Jones[32] have prepared the 1 - hydroxy - and the 6- and 8- methyl - 1 - hydroxyquinolizinium salts, respectively. Fozard and Jones[33] have also prepared 2 - hydroxyquinolizinium salts. Schraufstätter[34] discovered a simple synthesis of 3 - hydroxyquinolizinium salts (XXXII) which gave high yields. The quaternary salt (XXXI) between chloracetone and 2 - diethoxymethylpyridine was cyclised, by boiling under reflux with 48% hydrobromic acid, to give the 3 - hydroxy bromide (XXXII; X = Br).



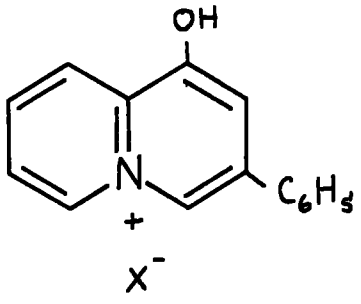
(XXXI) (XXXII)

It has also been prepared[35] by quaternising 2 - (1,3 - dioxolan - 2 - yl) pyridine with bromoacetone and cyclising the intermediate with hydrobromic acid.

Krohnke et. al.[36,37] have reported the preparation of 1 - hydroxyquinolizinium salts. Quaternisation of 2 - acetylpyridine with phenacyl bromide and subsequent treatment of the resulting pyridinium salt (XXXIII) with alkali gave the 1 - hydroxy-salt, isolated as the phenolic betaine having a zwitterion structure. Treatment of this with hydrobromic acid gave 1 - hydroxy - 3 - phenylquinolizinium bromide (XXXIV; X = Br) in high yield.



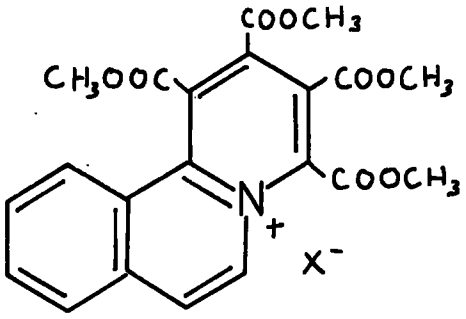
(XXXIII)



(XXXIV)

BENZOQUINOLIZINIUM SALTS

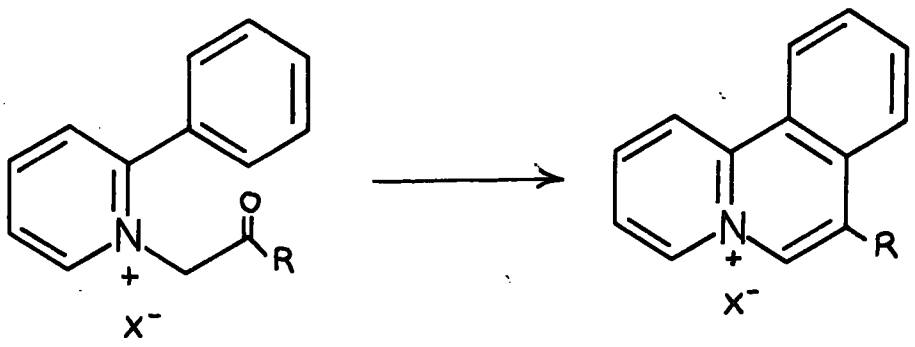
All three fully aromatic benzoquinolizinium salts have been prepared, both unsubstituted and with various alkyl and aryl substituents. Diels et. al.[5,38] treated isoquinoline with esters of acetylene dicarboxylic acid and obtained compounds containing the benzo [a] quinolizinium nucleus (XXXV; X = ClO_4 or Br).



(XXXV)

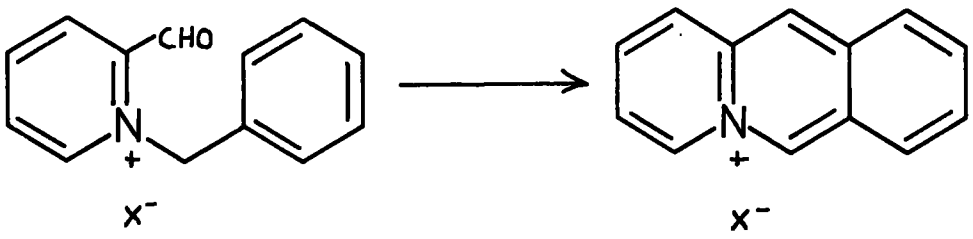
Besides the methods previously described for synthesis of quinolizinium salts, intramolecular cyclodehydration[39] is one of the more important preparative methods used for the synthesis of benzoquinolizinium salts.

The first fully aromatic benzo [a] quinolizinium[40] salts were prepared by Bradsher and Beavers[41] in 1954. Quaternisation of 2 - phenylpyridine with acyl and phenacyl halides at room temperature, and subsequent cyclodehydration with hydrobromic acid produced the benzo [a] quinolizinium bromides (XXXVI; R = CH_3 or C_6H_5; X = Br).



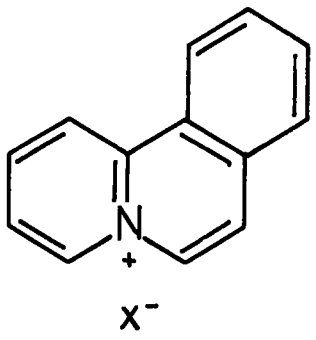
(XXXVI)

Aromatic cyclodehydration obviates the necessity for dehydrogenation and is suited for the synthesis of compounds which are not resistant to high temperatures. Using a modification of the above procedure, the same workers[42] synthesised hitherto unknown benzo [b] quinolizinium salts (XXXVII) by the cyclodehydration, with boiling hydrobromic acid, of the quaternary salt formed between benzyl bromide and pyridine - 2 - aldehyde.

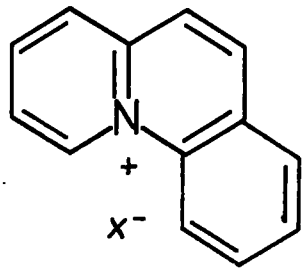


(XXXVII)

The above synthesis was extended by Bradsher and Jones[43] to the preparation of 8- methoxy - and some 7,8- and 8,9- dialkoxy derivatives. Glover and Jones[44] reported and synthesis of all three benzoquinolizinium salts (XXXVII), (XXXVIII) and (XXXIX) from the appropriate-cyanoquinolines and -cyanoisoquinolines using the method previously described on p. 10.



(XXXVIII)

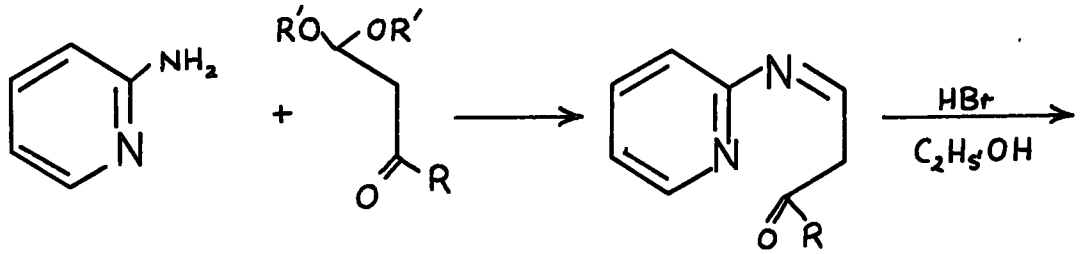


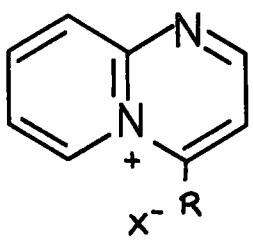
(XXXIX)

Bradsher et. al.[45,46,47,48,49,50,51,52] prepared many substituted benzo [b] quinolizinium salts.

BICYCLIC AZAQUINOLIZINIUM SALTS

At the time of writing this review no unsubstituted azaquinolizinium salts have been reported but alkyl- and aryl- substituted salts have been prepared. Nesmeyanov et. al.[53] synthesised 4 - alkyl - 1 - azaquinolizinium salts (XL) by heating 2 - aminopyridine with the appropriate acylacetal. The 2 - acylanil was then cyclised with ethanolic hydrobromic acid.

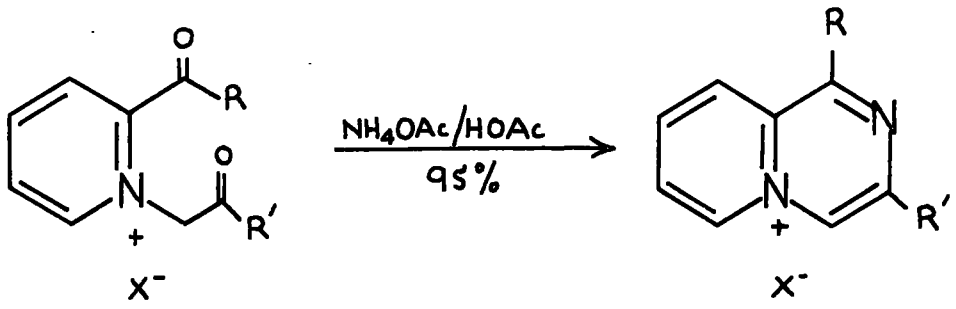




(XL)

A direct synthesis of 4 - substituted 1 - azaquinolizinium salts (XL; R = CH_3, X = ClO_4), in 80% yield, has been reported by Nesmeyanov and Rybinskaya[54] who treated 2 - aminopyridine with 2 - halovinyl ketones in methanolic perchloric acid. Krohnke[36,37] has recently described a general synthesis of 1,3 - disubstituted 2 - azaquinolizinium salts (XLI).

This synthesis involves cyclisation of the quaternary salt, formed between 2 - acylpyridines and phenacyl halides, by boiling under reflux with ammonium acetate in acetic acid as solvent.

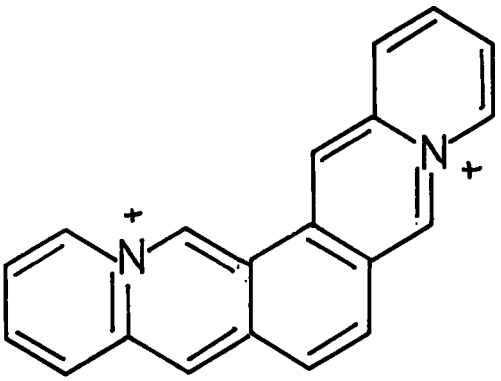


(XLI)

The above authors have also synthesised 1 - hydroxy - 3 - phenyl - 2 - azaquinolizinium salts by quaternising 2 - picolinic acid amide or 2 - cyanopyridine with phenacyl bromide in acetonitrile as solvent.

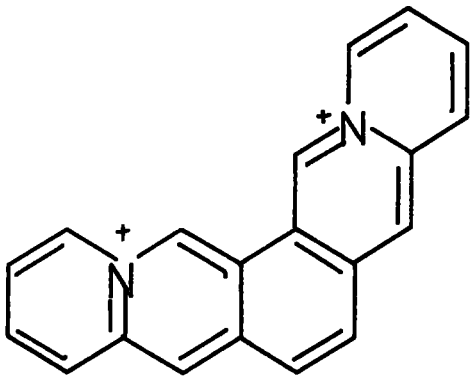
DIAZONIAPENTAPHENE SALTS

The first fully aromatic fused ring systems containing two quaternary bridgehead nitrogen atoms were synthesised by Bradsher and Parham[55]. They cyclised the quaternary salts formed, between 2- (1,3 - dioxolan - 2 - yl) pyridine and the appropriate 1,1' - dibromoxylene in tetramethylene sulphone, by treatment with polyphosphoric acid, yielding the isomeric diazoniapentaphine salts (XLII), (XLIII) and (XLIV).



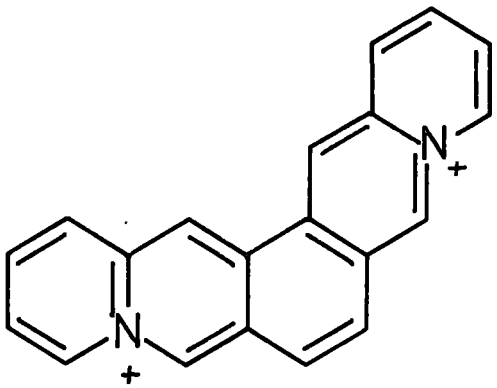
$2\,X^-$

(XLII)



$2\,X^-$

(XLIII)

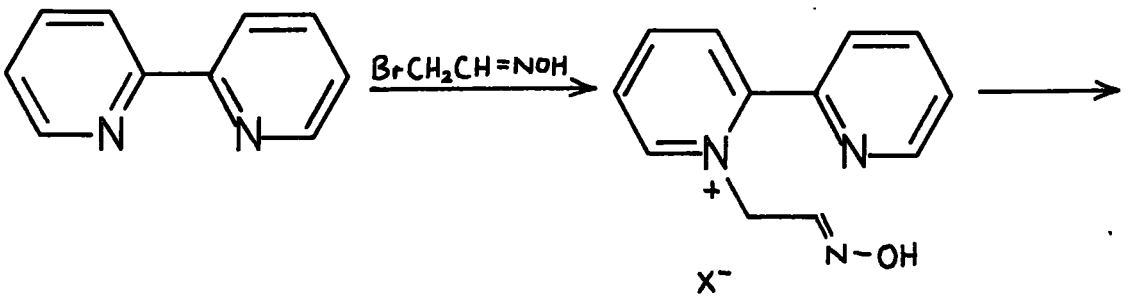


$2\,X^-$

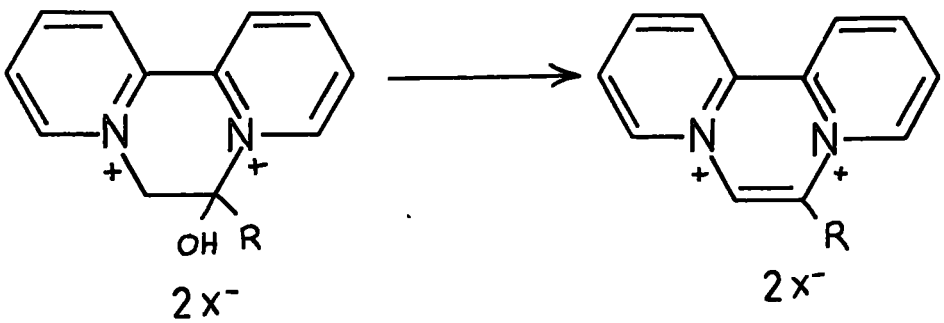
(XLIV)

DIPYRIDOPYRAZIDIINIUM SALTS

Corr and Glover[56,57] synthesised dipyrido [1,2 - a:2',1' - c] pyrazidiinium salts (XLVII; R = H) by cyclising, with hydrobromic acid, the quaternary salt (XLV;) formed between 2, 2' - bipyridyl and bromoacetaldehyde oxime; subsequent dehydration of the resulting hydroxy compound (XLVI; R = H) was achieved with phosphorus tribromide.



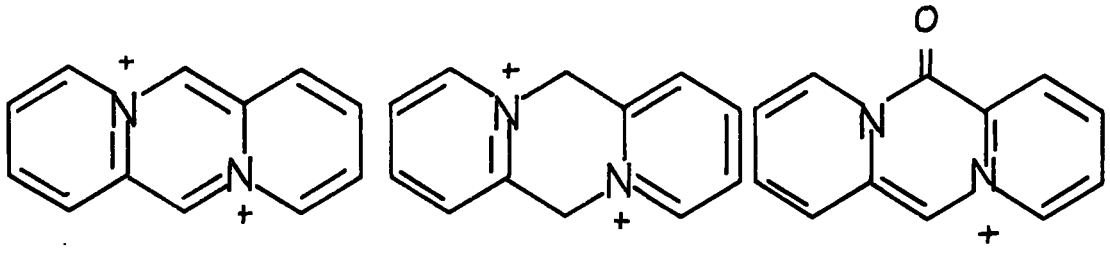
(XLV)



(XLVI) (XLVII)

The above authors[56,57] also synthesised the 6- methyl and 6- phenyl derivatives of (XLVII). Calder and Sasse[58] have simultaneously reported the synthesis of the 6- methyl derivative (XLVII; R = CH_3) and also the unsubstituted salt (XLVII; R = H).

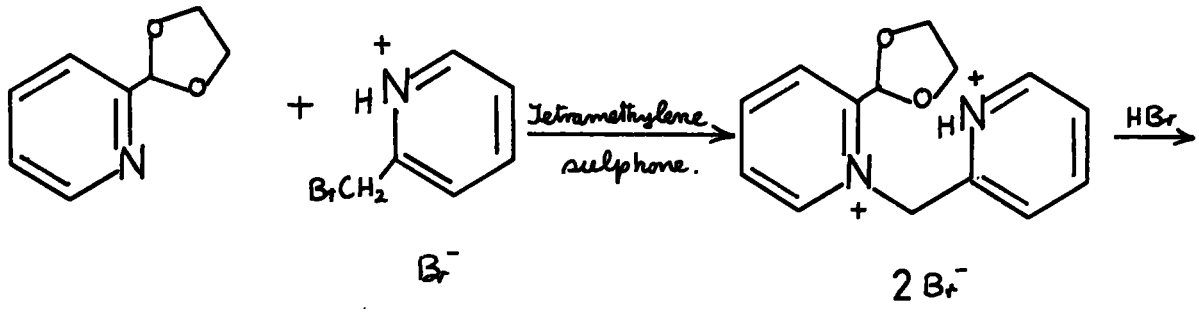
Glover and Morris[59] recently reported attempts to obtain the fully aromatic diquaternary system (XLVIII) by oxidation of the dihydroquaternary salts (XLIX) but obtained instead the lactam (L).



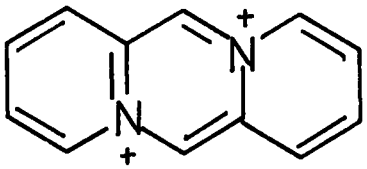
$2X^-$ $2X^-$ X^-

(XLVIII) (XLIX) (L)

These workers[60,61] have now synthesised the aromatic diquaternary system (XLVIII) by cyclising, with hydrobromic acid, the quaternary salt (LI) formed between 2 - (1,3 - dioxolan - 2 - yl) pyridine and 2 - pyridylmethyl bromide hydrobromide.



(LI)



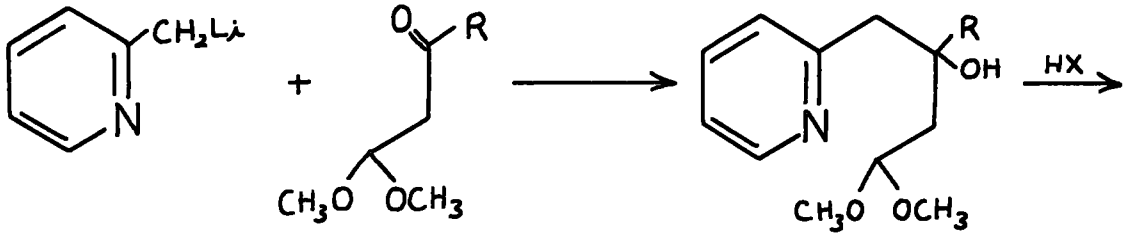
2 Br^-

(XLVIII)

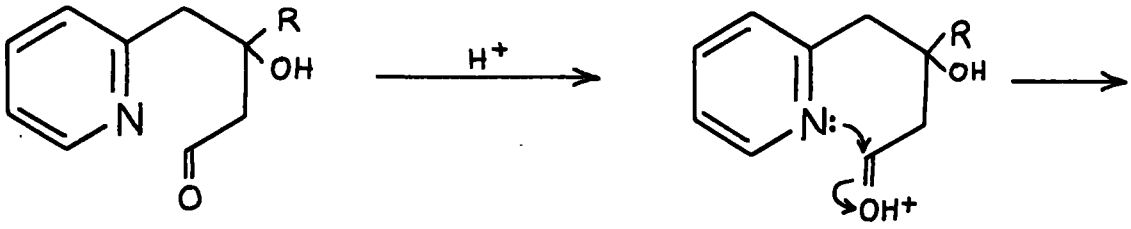
DISCUSSION

The "Diene synthesis" was used by Diels and Alder[5] to synthesise compounds containing the quinolizinium nucleus, but its application is limited to a few compounds because of the instability of the addition products formed and of their facile conversion to indolizine derivatives. Excluding this synthesis there are essentially two methods by which the quinolizinium ion can be synthesised. The first of these involves attachment of a suitable side chain to the carbon atom adjacent to the nitrogen atom of pyridine, followed by ring closure onto the pyridine nitrogen atom. The second method involves the quaternisation of a 2 - substituted pyridine with an alkyl halide containing a group capable of condensing with the 2 - substituent. These two general procedures are briefly outlined below.

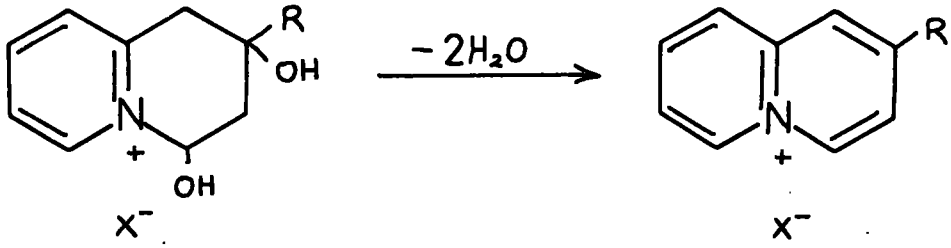
The first is typified by formation of 2 - substituted quinolizinium salts as described by Nesmeyanov and Rybinskaya[26]. Condensation of 2- picolyl - lithium with a 2- acylacetal gave the tertiary alcohol (LII), subsequent treatment with mineral acid giving the corresponding aldehyde (LIII). Cyclisation of the aldehyde probably occurs via protonation of the carbonyl oxygen atom, subsequent donation of the nitrogen lone pair onto the electron defficient carbon atom giving the alcohol (LIV). Dehydration of this occurs by the usual mechanism giving the fully aromatic quinolizinium ion (XXVII).



(LII)

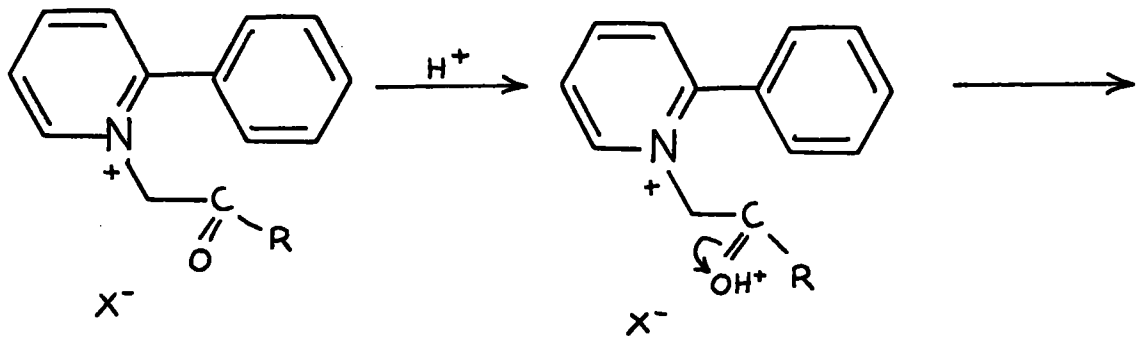


(LIII)

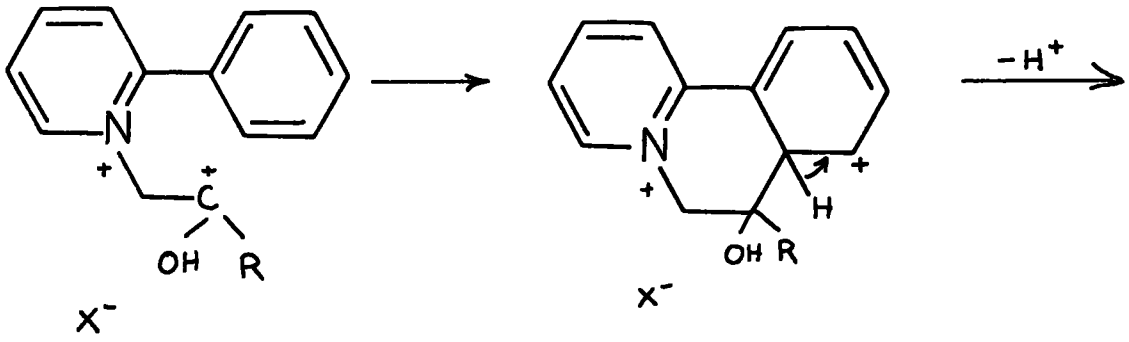


(LIV) (XXVII)

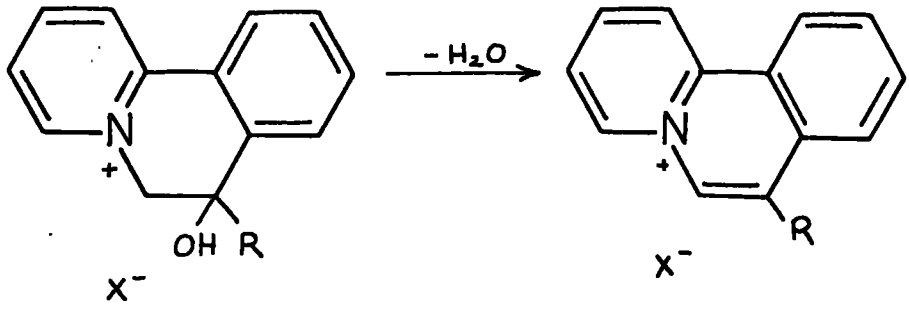
The second method is one of intramolecular cyclodehydration. The term cyclodehydration is used to describe the type of cyclisation in which the elements of water are eliminated from a compound, with the establishment of a new ring system; this procedure being first recorded by Bradsher and Schneider[62]. Cyclodehydration has the advantage of being simple and of general applicability to the synthesis, in high yield, of quinolizinium salts containing additional fused rings. The procedure is exemplified by the formation of benzo [a] quinolizinium salts as described by Bradsher and Beavers[41]. The reaction proceeds via protonation of the carbonyl oxygen atom of the quaternary salt (LV); electron withdrawal from the carbonyl double bond towards the oxygen atom then yielding the carbonium ion (LVI). An electrophilic attack of the latter onto the benzene ring occurs followed by loss of a proton to give the tertiary alcohol (LVII). Dehydration of the latter readily occurs to give the fully aromatic system (XXXVI).



(LV)

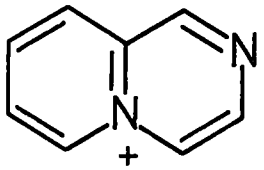


(LVI)



(LVII) (XXXVI)

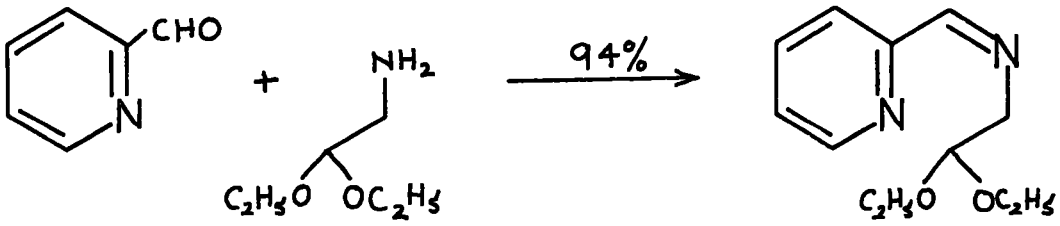
No unsubstituted pyrido [1,2-a] pyrazinium salts (I) have yet been prepared and their synthesis was therefore undertaken.



X^-

(I)

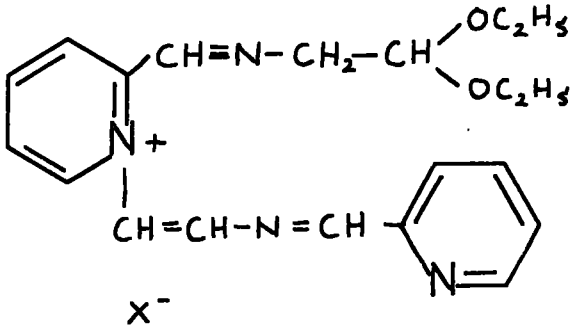
A convenient method for the synthesis of the parent salt (I) would be the cyclisation, in acid media, of the anil (LVIII) formed by the condensation between pyridine - 2 - aldehyde and aminoacetal[63].



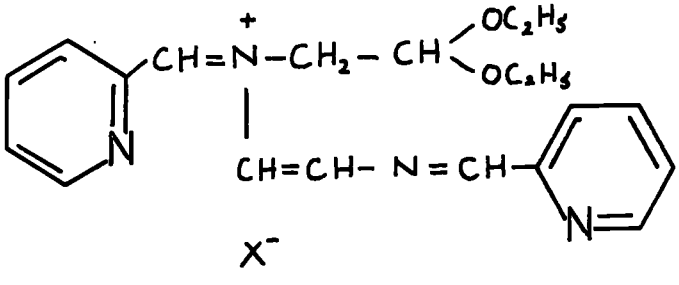
(LVIII)

The azomethine linkage is susceptable to hydrolysis by mineral acid, unless it is a member of an aromatic heterocyclic nucleus as in the thiazoles, and during attempts to prepare naphthyridine bases by cyclisation with acid catalysts, of the anils formed between pyridine aldehydes and aminoacetal, Hart[63] found that the reagents used resulted either in

cleavage of the azomethine system or gave dark brown resins from which no pure compound was isolated. However, Dadkhah and Prijs[64] prepared 2 - pyridyl - and 2 - quinolyloxazoles by the cyclisation of Schiff's bases of the type (LVIII), by treatment with concentrated sulphuric acid and subsequent neutralisation with alkali. To reduce the possibility of hydrolytic cleavage of the azomethine group, cyclisation of the anil (LVIII) to the parent pyrido [1,2 - a] pyrazinium system (I) was attempted by boiling it under reflux with alcoholic picric acid. The solid obtained had a molecular formula of $C_{26}H_{27}N_7O_9$. Assuming the formation of a monopicrate, the structure of the solid may be represented by either of the two formulae (LIX or LX; X = picrate) given below.



(LIX)

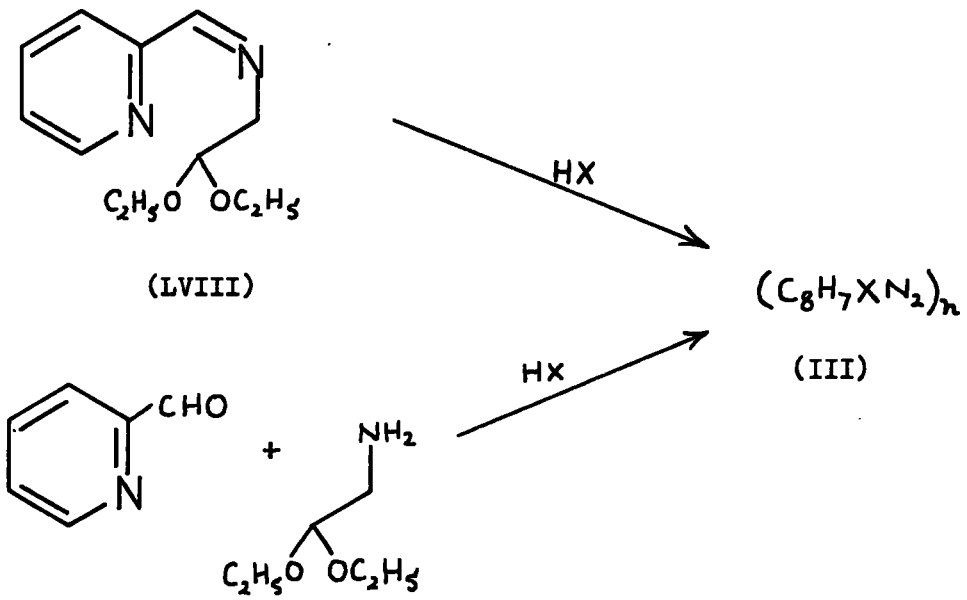


(LX)

Intermolecular, instead of intramolecular reaction of the anil (LVIII) occured in the presence of alcoholic picric acid. Conversion of the picrate (LIX or LX; X = picrate) to the bromide (LIX or LX; X = Br) was effected by passage of a methanolic solution of the former down an Amberlite I.R.A. - 400 (Br) anion exchange resin. The resulting bromide (LIX or LX; X = Br) showed absorption bands in the infrared region of the spectrum at 1595, 1510, 1475 and 745 cm^{-1} (pyridine ring vibrations), and four bands at 1170, 1115, 1068 and 1055 cm^{-1} which are specific for the presence of an acetal group[65] (C - O - C - O - C). The ultraviolet spectrum showed a single absorption maximum at 318mμ attributed to increased conjugation in the system. A band at 1650 cm^{-1} in the infrared spectrum was thus attributed to the presence of a conjugated diene.

THE ACTION OF CONCENTRATED MINERAL ACID ON THE ANIL (LVIII)

A further attempt to cyclise the anil (LVIII) was carried out by boiling it under reflux with concentrated halogen hydracids. Crystalline quaternary salts (III; X = Br or Cl) were isolated in 20-27% yield and the analytical data indicated a molecular formula of $(C_8H_7XN_2)_n$ (X = Br or Cl), from which it was assumed that they were the required pyrido [1,2-a] pyrazinium salts (I; X = Br or Cl). It was subsequently found that these same compounds could be obtained in slightly higher yields, 23-32%, by boiling pyridine - 2 - aldehyde and aminoacetal under reflux with concentrated halogen hydracids.

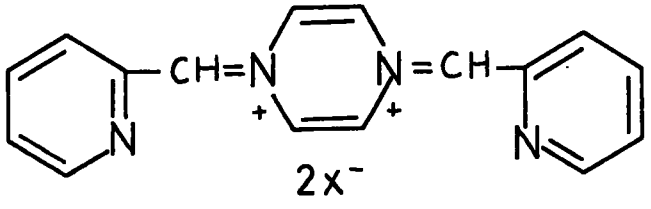


(LVIII)

(III)

However, the ultraviolet spectra of these salts showed no absorption maxima at wavelengths longer than 288mμ, whereas that of 1- azaquinolizinium salts, synthesised by Nesmeyanov et. al.[53] showed absorption maxima at 336, 318, 312, 304, 274 and 228mμ, closely resembling those obtained for the parent quinolizinium ion[8,9].

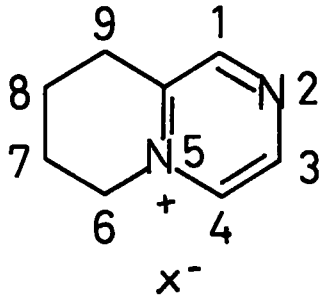
The n.m.r. spectrum of the bromide (III; X = Br) in deuterium oxide showed only a collection of protons in the region τ1.5 - 3.5 whereas consideration of the n.m.r. spectrum in deuterium oxide of 1 - methyl - 3 - phenylpyrido [1,2-a] pyrazinium bromide, prepared using the method described by Krohnke[36], showed that the aromatic protons directly attached to the heterocyclic nucleus gave rise to signals in the region τ0.6 - 1.8. The structure (I) is, therefore, inconsistent with its spectroscopic properties, hence the N,N - di - (2 - pyridylmethylene) pyrazidiinium dihalide (III) structure was considered.



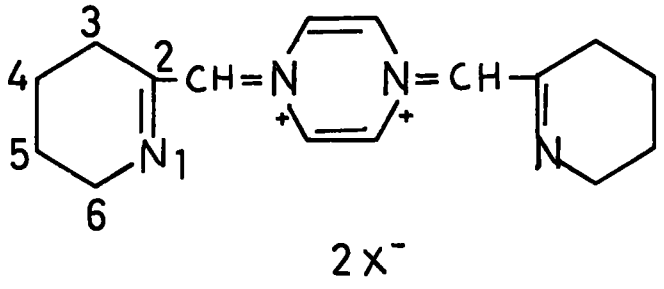
(III)

An attempt to determine the molecular weight of the salts by osmometry gave no satisfactory results. Further, catalytic hydrogenation of these salts under a variety of conditions, did not produce the expected perhydropyrido [1,2-a] pyrazine (II), but gave instead salts, the

analytical data for which, indicated a molecular formula of $(C_8H_{11}XN_2)_n$ (X = Br or Cl). The infrared spectra of these salts contained no bands attributable to ($\overset{+}{N}H$) absorption, and no organic material could be extracted from a basified aqueous solution of the salts. It was concluded, therefore, that the salts were quaternary and possible structures consistent with the analytical data are the 6,7,8,9 - tetrahydropyrido [1,2-a] pyrazinium halide system (LXI), and the diquaternary system (LXII).



(LXI)



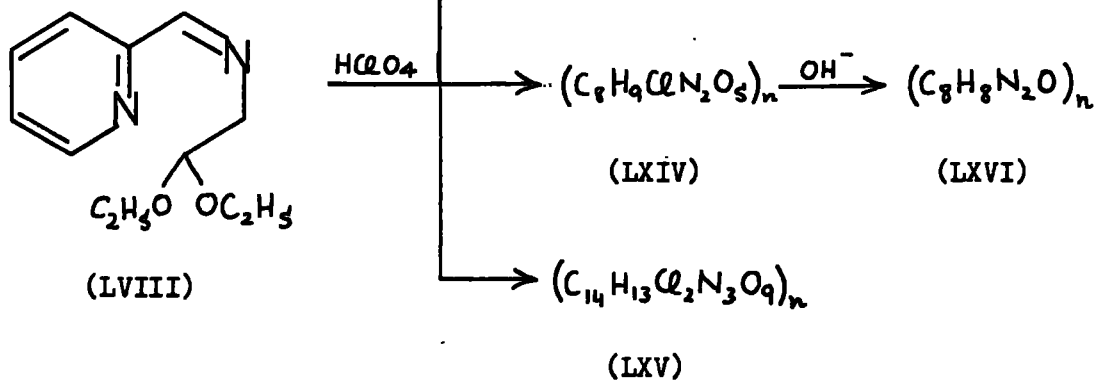
(LXII)

The infrared spectrum of the product of hydrogenation indicated an unsaturated structure and this was confirmed by the ultraviolet absorption spectrum which showed a single maximum at 225mμ . The principal ultraviolet absorption maximum of pyrazine is at 260mμ ,[66] thus precluding the quaternary pyrazinium structure (LXI). The diquaternary structure (LXII) is only acceptable if it is assumed that the largest effective chromophore in such a system extends only between the azomethine and the quaternary nitrogen atoms, i.e. the positively charged nitrogen atom isolates the terminal unsaturated system.

The n.m.r. spectrum in deuterium oxide of the hydrogenation product (LXII; X = Br) showed two triplets centred at τ5.8 and τ7.05 attributable to the methylenic protons on C_6 and C_3 respectively of the proposed structure (LXII) and a multiplet centred at τ7.95 attributable to the protons on C_4 and C_5. The spectrum contained two other signals at τ 2.6 and τ4.2 only attributable to the protons on the exocyclic carbon atom and the protons of the central ring respectively. The integrated spectrum showed that the ratio of non equivalent hydrogen atoms was consistent with the above formula (LXII), However, the positions of the signals at τ2.6 and τ4.2 and the unsplit nature of the signal at τ4.2 are not entirely consistent with the suggested structure. Further, the resistance of the hydrogenation product to complete hydrogenation is also apparently incompatible with the structure (LXII).

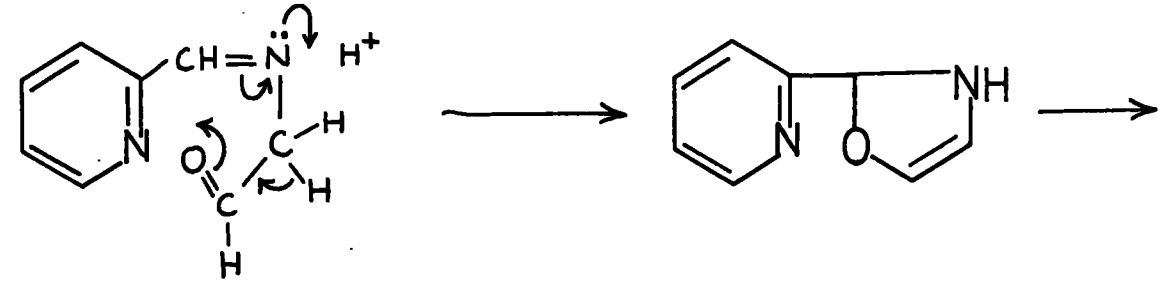
THE ACTION OF PERCHLORIC ACID ON ACETALDEHYDE - (2- PYRIDYLMETHYLENEAMINO) DIETHYLACETAL (LVIII).

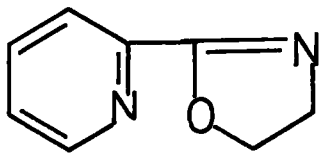
A solution of the anil (LVIII) in 58% perchloric acid was heated on a boiling water bath for 24 hr., three products being isolated from the reaction mixture. The first, a solid (LXIII) which precipitated from the hot solution was filtered and shown to be the perchlorate (III; X = ClO_4) corresponding to the bromide and chloride (III; X = Br or Cl) previously described. Addition of ethanol to the filtrate gave a yellow solid which was filtered and which crystallised from aqueous methanol as colourless plates (LXIV). Evaporation of the filtrate to near dryness gave a third compound (LXV) which crystallised from water as yellow prisms. The properties and possible structure of the last compound are discussed later (p. 61).



Analytical figures for the second compound (LXIV) indicated a molecular formula of $(C_8H_9ClN_2O_5)_n$ and its infrared spectrum showed bands centred at 3100cm^{-1} $(\overset{+}{N}H)$[67] and 1090cm^{-1} (ClO_4^-)[68] indicating that it was a hydroperchlorate salt.

Basification of the salt yielded the corresponding free base (LXVI) and the analytical data for this and for its derived picrate indicated a molecular formula of $(C_8H_8N_2O)_n$. The infrared spectrum of this base (LXVI) showed bands at 1595, 1500, 1485 and 760cm^{-1} (pyridine ring vibrations) and a possible structure for the base was thought to be 2 - pyridyl - Δ^2 - oxazoline (LXVII) produced according to the scheme :-

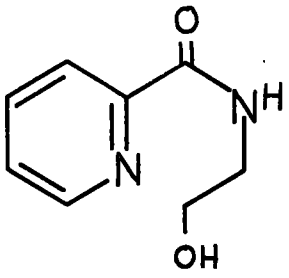




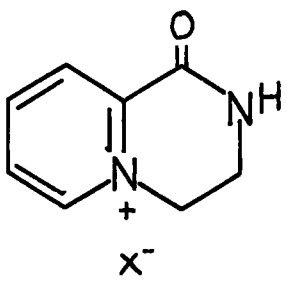
(LXVII)

The final double bond shift being suggested to account for the absence, in the infrared spectrum, of a band attributable to $\geq$NH absorption.

Attempts to synthesise the 2 - pyridyl - Δ^2 - oxazoline (LXVII) unambiguously from N- (2- hydroxyethyl) - 2 - picolinamide (LXVIII) and p - toluenesulphonyl chloride, using the methods described by Boyd and Hansen[69] and Boyd and Rittner[70], were unsuccessful, the only isolated product being the quaternary chloride (LXIX; X = Cl).

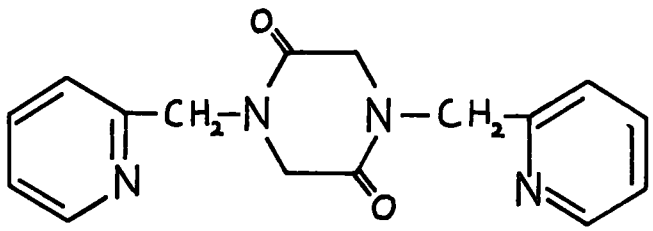


(LXVIII)



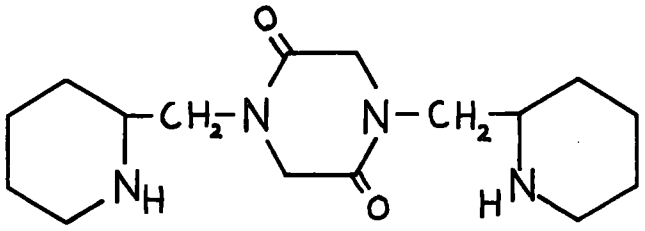
(LXIX)

The n.m.r. spectrum of the base (LXVI) in deuterochloroform showed peaks corresponding to those of a 2- substituted pyridine and two unsplit methylene proton peaks at $\tau 5.3$ and $\tau 5.8$; the ratio of aromatic to methylene protons being 1:1. The unsplit nature of the methylene proton signals precludes the 2 - pyridyl - Δ^2 - oxazoline structure (LXVII) for the base (LXVI). Consideration of the n.m.r. spectrum in conjunction with the infrared spectrum which showed a strong band at 1650cm^{-1} attributable to the carbonyl group of a six membered dilactam[71], and with the ultraviolet absorption spectrum which showed absorption maxima at 269, 262 and 257mμ, closely resembling that of 2 - picoline, indicated the dilactam structure (LXVI) for the base.



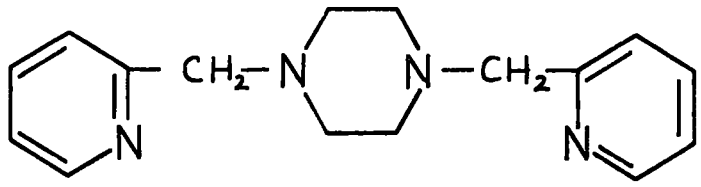
(LXVI)

The structure of the dilactam (LXVI) was confirmed by molecular weight studies; values of 296, 289 and 296 being obtained by ultraviolet spectrophotometric measurements on the dipicrate[72], by osmometry and from the mass spectrum of the free base respectively. Hydrogenation of the dilactam (LXVI) to completion gave the fully saturated dilactam (LXX).



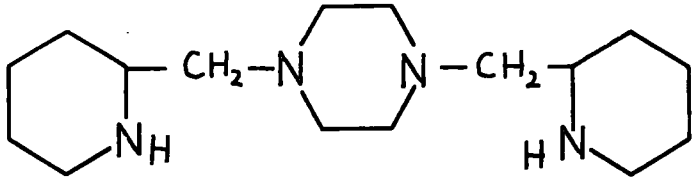
(LXX)

Reduction of the dilactam (LXVI) with lithium aluminium hydride gave the corresponding base (LXXI).



(LXXI)

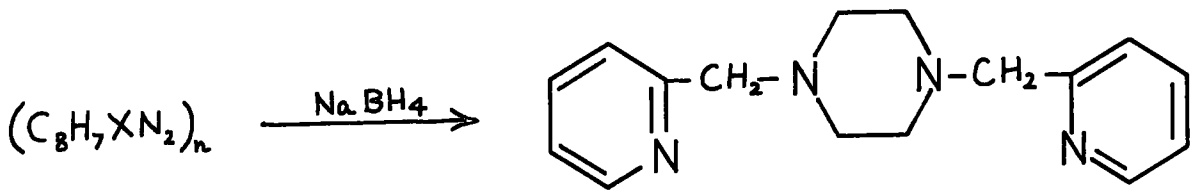
The structure of this base was confirmed spectroscopically. The ultraviolet absorption spectrum again resembled that of 2- picoline and the n.m.r. spectrum in deuterochloroform showed peaks characteristic of a 2- substituted pyridine together with a four proton singlet at $\tau 6.3$ corresponding to the methylene groups adjacent to the pyridine ring and an eight proton singlet at $\tau 7.4$ corresponding to the protons of the central piperazine ring. The molecular weight of the base as determined by ultraviolet spectrophotometric measurements on the tetrapicrate[72] and from the mass spectrum of the free base was 268; catalytic hydrogenation of the base (LXXI) gave the perhydrobase (IV).



(IV)

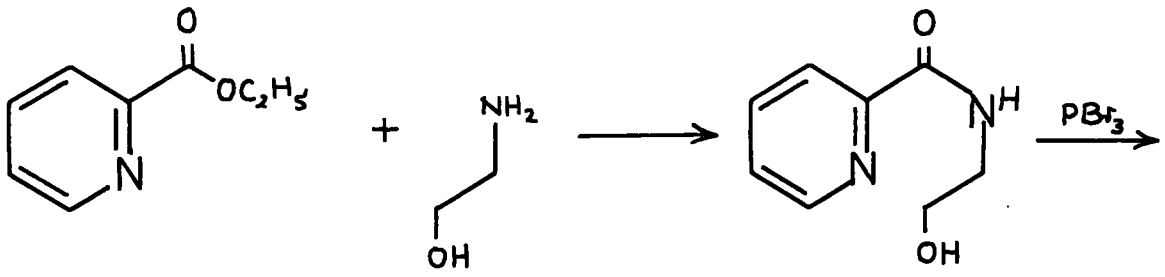
Reduction of the dilactam (LXX) with lithium aluminium hydride also gave the above perhydro base (IV).

As described previously (p. 37) attempts to hydrogenate to completion the quaternary salt (III) obtained by the action of concentrated aqueous acids on the anil (LVIII), were unsuccessful. However, reduction of the quaternary salt (III; X = Cl) with sodium borohydride in aqueous methanol gave N,N - di - (2- picolyl) perhydropyrazine (LXXI) identical with the sample previously described and obtained by the reduction of the dilactam (LXVI) with lithium aluminium hydride.

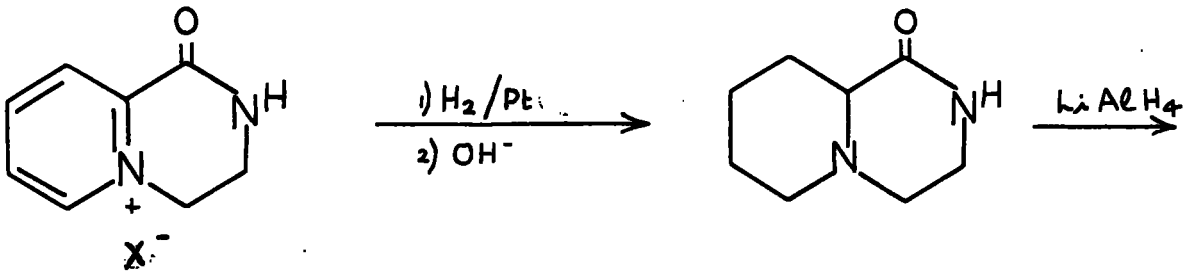


(III) (LXXI)

In connection with this section of the work perhydropyrido [1,2-a] pyrazine (II) was at one stage required as a model and was prepared unambiguously from ethyl picolinate and ethanolamine using the reaction sequence outlined below.

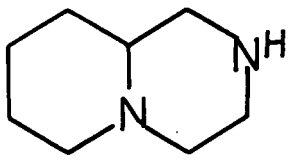


(LXVIII)



(LXIX)

(LXXII)

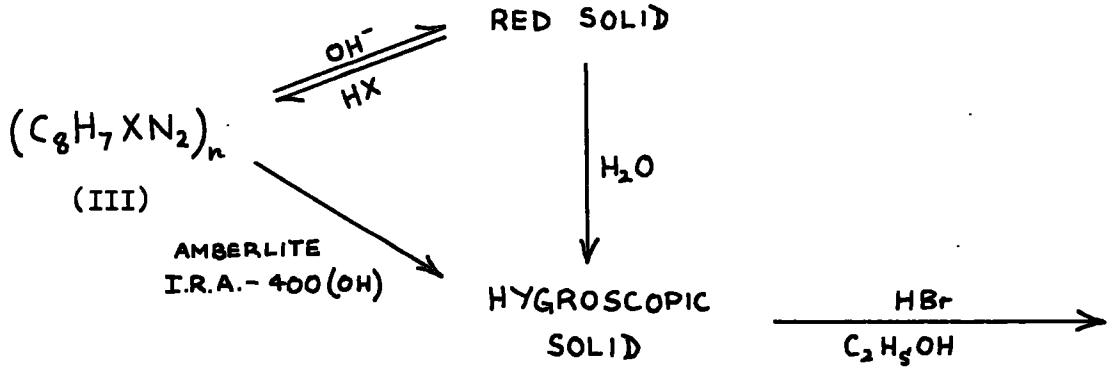


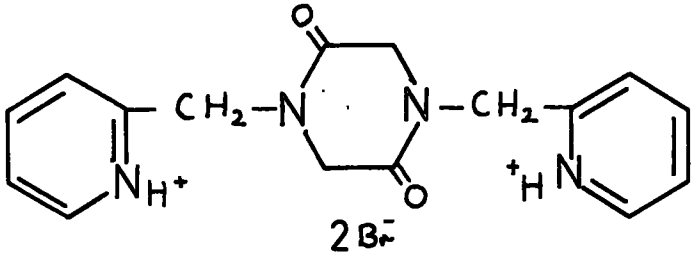
(II)

The melting point of the dihydrochloride salt of the base (II) was 208 - 211°, in good agreement with that recorded by Freed and Day[73] and Winterfeld et. al.[74]. The melting point of the base dipicrate was, however, 275 - 278°, markedly different from the value of 240° and 250 - 260° (decomp.) recorded by Winterfeld et. al.[74,75]

THE ACTION OF ALKALI ON THE QUATERNARY SALT $(C_8H_7XN_2)_n$, [PROBABLY THE N,N- DI - (2- PYRIDYLMETHYLENE) PYRAZIDIINIUM DIHALIDE (III; X = Br OR Cl)]

Treatment of an aqueous solution of the quaternary salt (III; X = Br or Cl) with concentrated sodium hydroxide gave a crimson solid, presumably a sodium salt; the reaction was reversed by the addition of concentrated acid to the red solid. Purification of the red solid was impractible since the dried solid became warm and rapidly darkened on exposure to the atmosphere. An aqueous solution of the red solid when boiled under reflux and subsequently evaporated to dryness gave a hygroscopic residue which, when dissolved in ethanolic hydrobromic acid and warmed was converted into the dihydrobromide (LXXIII) of the dilactam (LXVI).





(LXXIII)

The corresponding free base (LXVI) and its derived dipicrate were identical with the samples previously described. It was found later that the reaction was best carried out by passing an aqueous solution of the quaternary salt (III), down a strongly basic ion exchange column, evaporating the eluant to dryness and warming the residue with alcoholic hydrobromic acid.

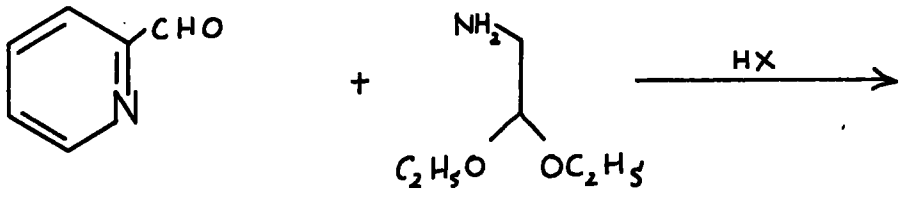
SUMMARY

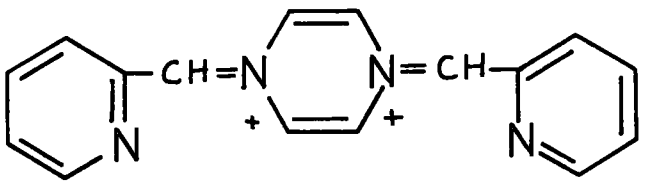
It is considered that the evidence so far recorded shows that the salts (III) are not pyrido [1,2-a] pyrazinium salts (I) and indicates strongly though not conclusively, that they are N,N- di -(2 - pyridylmethylene) pyrazidiinium salts (III).

A summary of the reactions so far described, together with the possible intermediatesis given below.

1. FORMATION OF THE SALTS $(C_8H_7XN_2)_n$ (III)

(a)

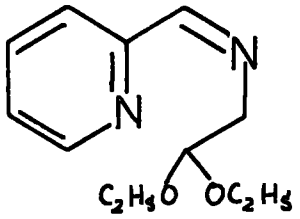




$2X^-$

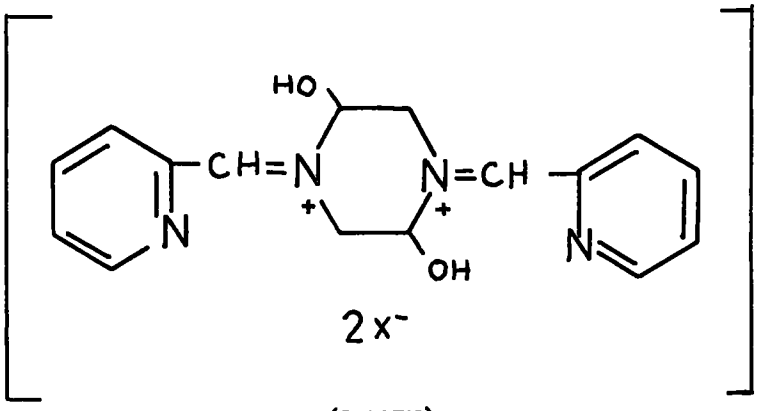
(III)

(b)

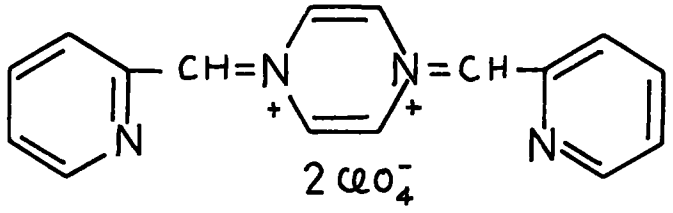


$HClO_4$

(LVIII)

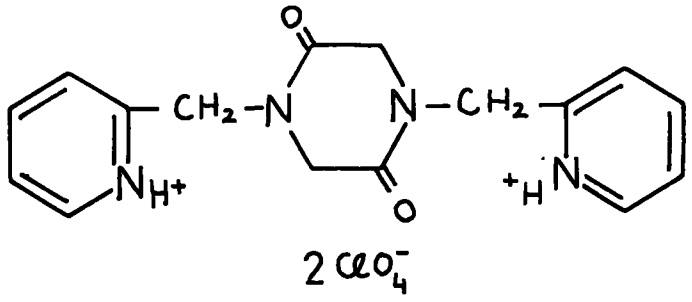


(LXXIV)



(LXIII)

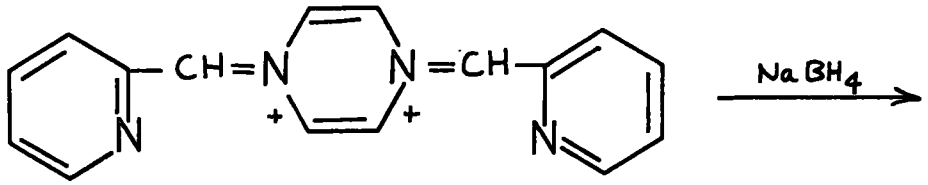
+



(LXIV)

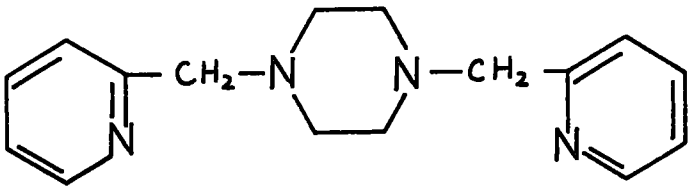
The isolation of two products in the case of reaction (b) suggests the formation of the common intermediate (LXXIV).

2. REDUCTION OF THE SALTS $(C_8H_7XN_2)_n$ (III; X = Br or Cl) WITH SODIUM BOROHYDRIDE.



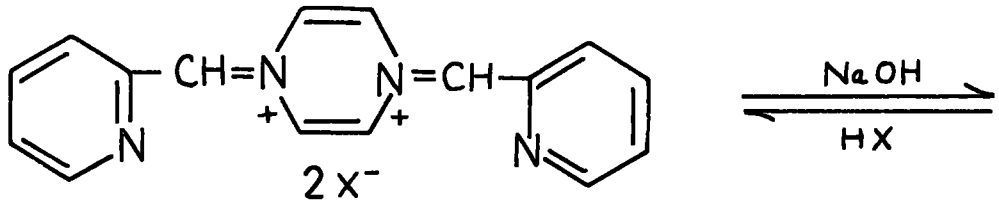
$2\ X^-$

(III)

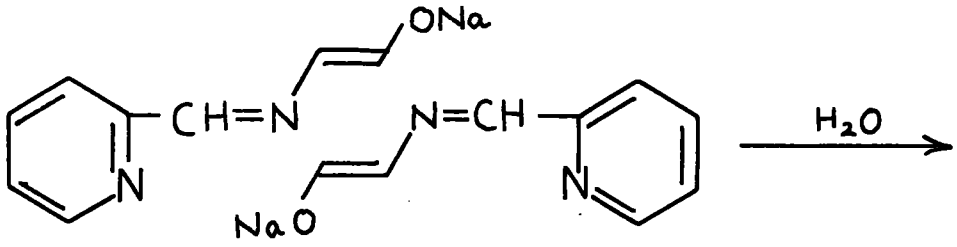


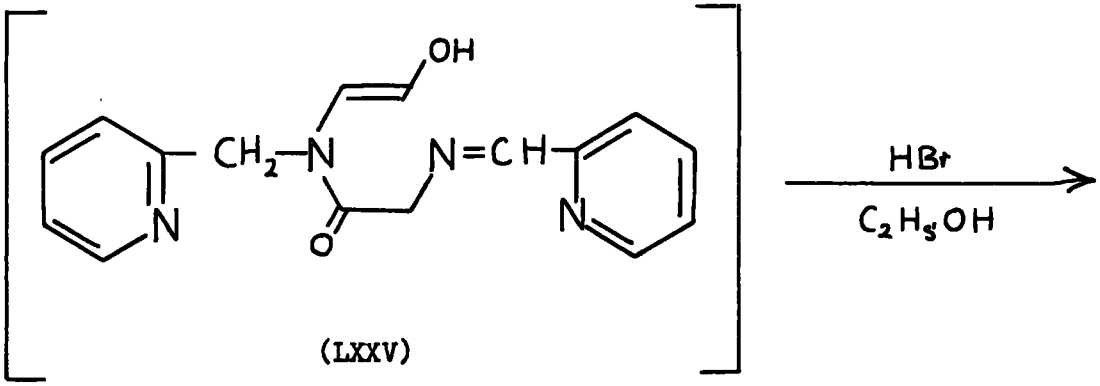
(LXXI)

3. THE ACTION OF ALKALI ON THE SALTS $(C_8H_7XN_2)_n$ (III; X = Br or Cl)

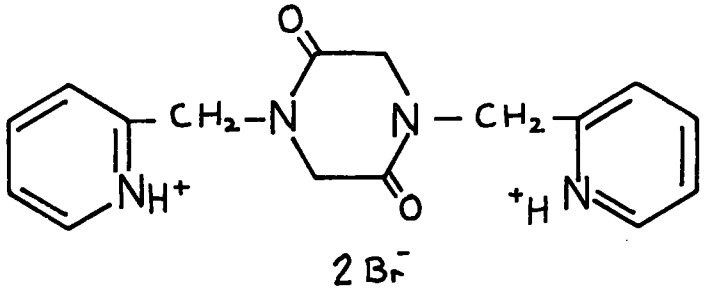


(III)



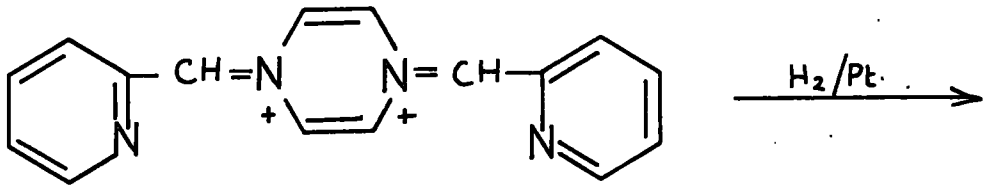


(LXXV)

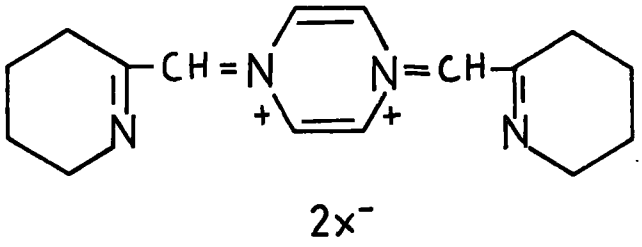


(LXXIII)

4. HYDROGENATION OF THE SALTS $(C_8H_7XN_2)_n$ (III; X = Br or Cl)



(III)

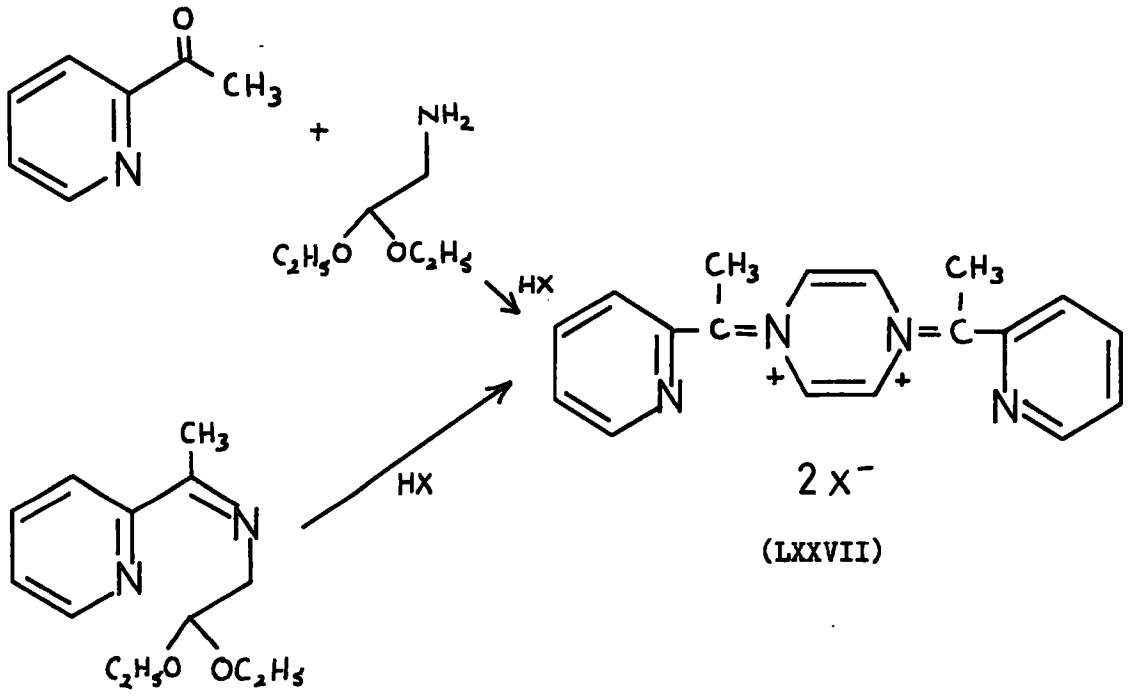


(LXII)

Facts not entirely consistent with the di quaternary structure suggested for the salts (III) are its spectroscopic properties and the spectroscopic properties of its hydrogenation product (LXII). The resistance of its hydrogenation product to further hydrogenation is also difficult to explain. In view of these anomalies it was decided to study the products of condensation under similar conditions, between 2- acetylpyridine and aminoacetal and between pyridine - 2 - aldehyde and 2 - bromoethylamine hydrobromide.

THE CONDENSATION OF AMINOACETAL WITH 2 - ACETYLPYRIDINE

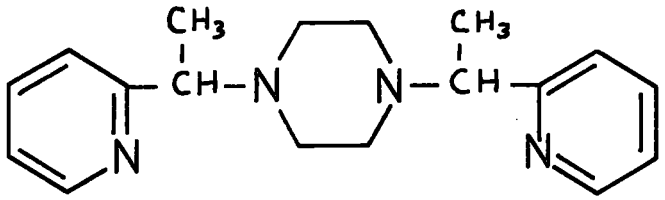
In the absence of acids condensation of aminoacetal with 2 - acetylpyridine gave the expected anil (LXXVI). Cyclisation of this anil in concentrated aqueous acid or condensation of aminoacetal with 2 - acetylpyridine in the presence of concentrated aqueous acid gave quaternary salts, the spectroscopic properties and analytical data for which showed them to be the methyl derivatives (LXXVII) of the quaternary salts (III) previously described.



(LXXVII)

(LXXVI)

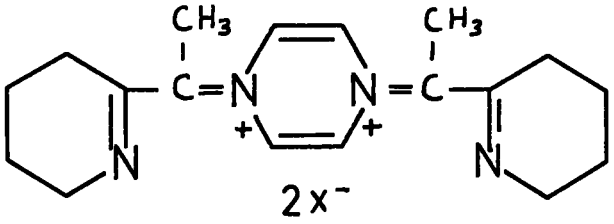
Reduction of the quaternary salt (LXXVII) with sodium borohydride gave the base (LXXVIII), the analytical data and n.m.r. spectrum of which showed clearly that it was the dimethyl derivative of the base (LXXI).



(LXXVIII)

The n.m.r. spectrum in deuterochloroform showed the typical pattern of a 2 - substituted pyridine together with a two proton quartet centred at τ6.45 corresponding to the protons on the tertiary carbon atoms adjacent to the pyridine rings, an eight proton singlet at τ 7.5 corresponding to the protons of the central piperazine ring, and a six proton singlet at τ8,6 corresponding to the protons of the methyl groups.

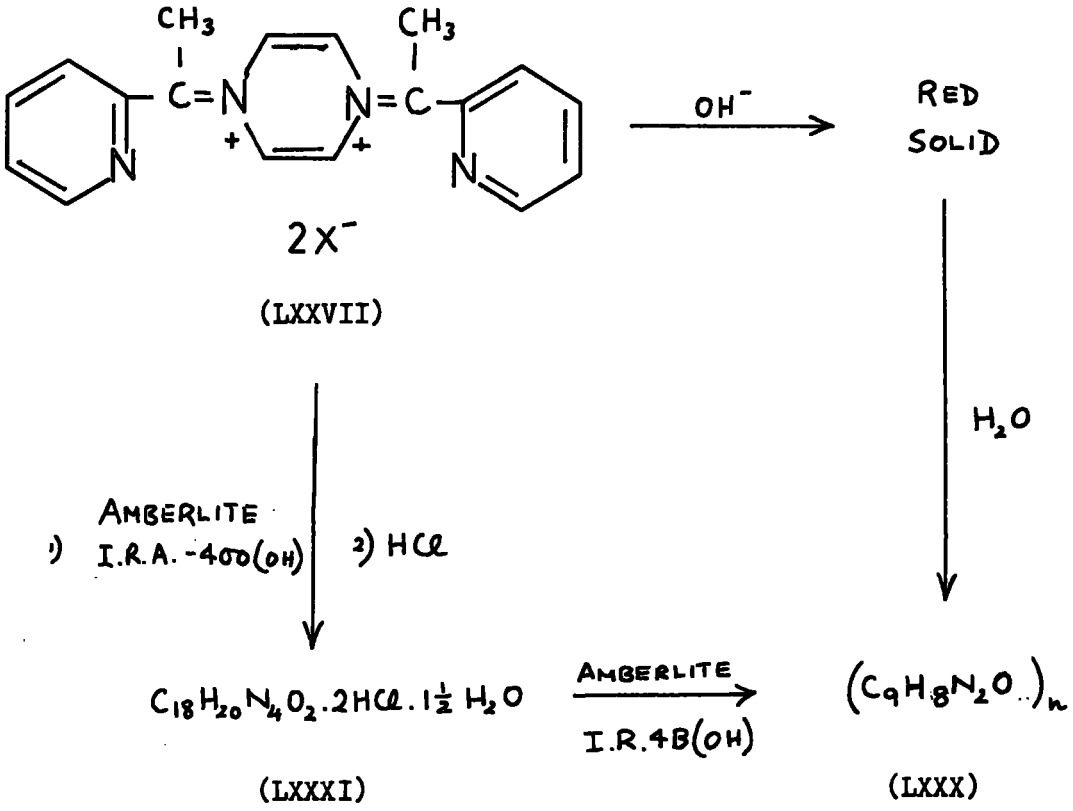
Hydrogenation of the methyl substituted quaternary salts (LXXVII) gave an unsaturated compound probably (LXXVIX) which was clearly the dimethyl derivative of the unsaturated compound for which the structure (LXII) has been suggested.



(LXXVIX)

Further, in the n.m.r. spectrum of the diquaternary salt (LXXVIX) the peaks initially assigned to the protons on the exocyclic carbon atoms in the unsubstituted compound (LXII) were missing and a six proton peak was observed at $\tau 7.85$ and attributed to the protons of the methyl groups. However, the occurence of a four proton signal only attributable to the protons of the central ring, with a τ value as high as 4.6 is apparently inconsistent with the above structure as also is the unsplit nature of this signal.

Treatment of the methyl substituted quaternary salt (LXXVII) with concentrated aqueous sodium hydroxide again gave a crimson solid, the reaction being reversed by the addition of concentrated mineral acid. The red solid when boiled with water and the water evaporated gave a white crystalline solid (LXXX) soluble in water and insoluble in ether. Analysis of the solid and of its derived dipicrate indicated a molecular formula of $(C_9H_{18}N_2O)_n$ where n is probably equal to two since the n.m.r. spectrum showed the presence of two non equivalent methyl groups. The same crystalline solid (LXXX) could be obtained by passing an aqueous solution of the methyl substituted quaternary salt (LXXVII) down a strongly basic ion exchange column and evaporating the eluate. Treatment of the residue with concentrated hydrochloric acid followed by addition of acetone precipitated a salt (LXXXI) which was converted to the free base (LXXX) by absorption of the acid on a weakly basic ion exchange column.

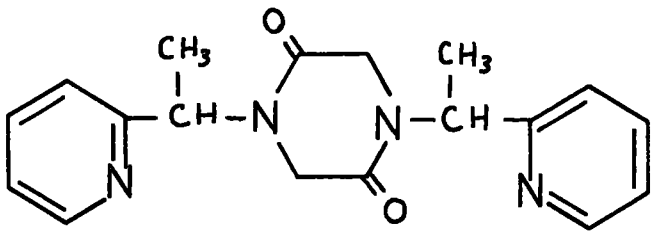


(LXXVII)

(LXXXI)

(LXXX)

The base (LXXX) was clearly not the dimethyl derivative (LXXXII) of the dilactam (LXVI) obtained by a similar series of reactions on the unsubstituted quaternary salt (III).

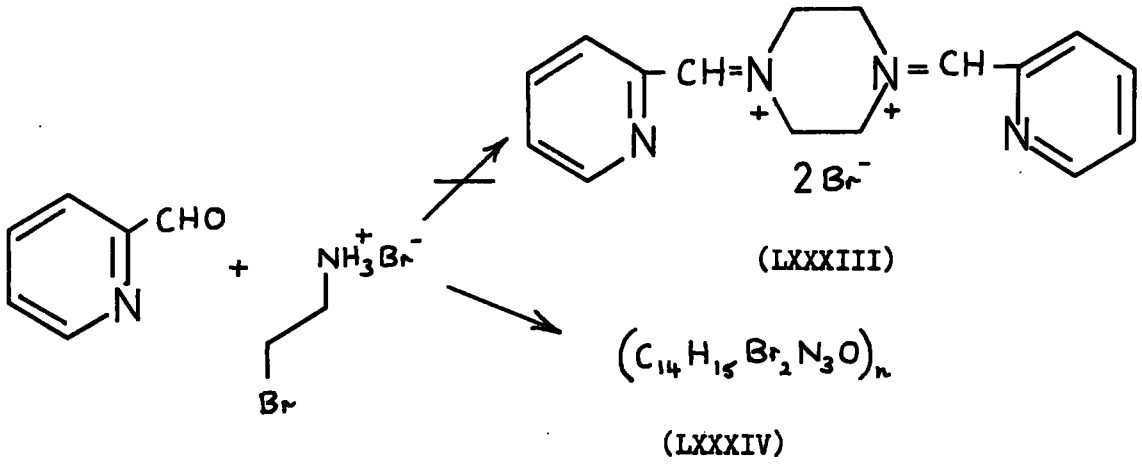


(LXXXII)

However, treatment of the base hydrochloride (LXXXI) with strong aqueous sodium hydroxide gave, in low yield, a compound assumed to be the dilactam (LXXXII) since its infrared spectrum was very similar to that of the unsubstituted dilactam (LXVI). The yield of dilactam was insufficient for an analytical sample to be obtained but the analytical figures of the derived dipicrate were consistent with the dilactam structure (LXXXII).

THE CONDENSATION OF PYRIDINE - 2 - ALDEHYDE WITH 2 - BROMOETHYLAMINE HYDROBROMIDE

By analogy with the reaction between aminoacetal and pyridine - 2 - aldehyde previously described, it was considered that the likely product of condensation between pyridine - 2 - aldehyde and 2 - bromoethylamine hydrobromide would be the diquaternary salt (LXXXIII).



Condensation in methanol as solvent or in aqueous hydrobromic acid gave instead of the expected diquaternary salt (LXXXIII), a compound (LXXXIV) the analytical data for which and for its derived picrate, indicated a molecular formula of $(C_{14}H_{15}Br_2N_3O)_n$ containing one less nitrogen atom than the diquaternary structure (LXXXIII). The n.m.r. spectrum of the compound (LXXXIV) showed a collection of protons in the region τ0.6 - 2.4 and a singlet at τ4.6 corresponding to the protons of a methylene group adjacent to a quaternary nitrogen atom[57]. The principal ultraviolet absorption maximum for the compound occured at 409mμ which is consistent with a higher degree of conjugation than is present in the diquaternary system (LXXXIII).

Hydrogenation of the compound (LXXXIV) gave an unidentified product the analytical figures for which indicated a molecular formula of $(C_{14}H_{21}N_3O_6)_n$.

THE ACTION OF ALCOHOLIC PICRIC ACID ON ACETALDEHYDE - (2 - PYRIDYLMETHYLENEAMINO) DIETHYLACETAL (LVIII)

As described on p.34 the picrate produced by the action of alcoholic picric acid on the anil (LVIII) had the molecular formula $C_{26}H_{27}N_7O_9$. The picrate was converted to the bromide by ion exchange and the infrared and ultraviolet spectroscopic properties of the bromide were apparently consistent with either of the formulations (LIX) or (LX) for these salts.

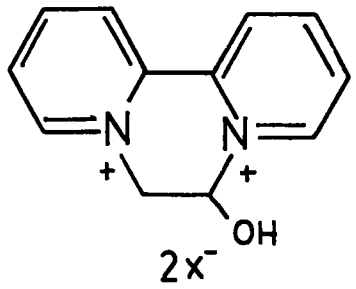
Treatment of this bromide with boiling concentrated hydrobromic acid followed by the addition of ethanol gave a quaternary salt (LXXXV) the analytical figures for which and for the corresponding perchlorate suggested a molecular formula of $(C_{14}H_{13}Br_2N_3O)$. The perchlorate salt was identical with the third salt (LXV) isolated from the reaction between perchloric acid and the anil (LVIII) (p.40).

$$C_{20}H_{25}BrN_4O_2 \xrightarrow{HX} C_{14}H_{13}X_2N_3O$$

(LIX or LX; X = Br) (LXXXV)

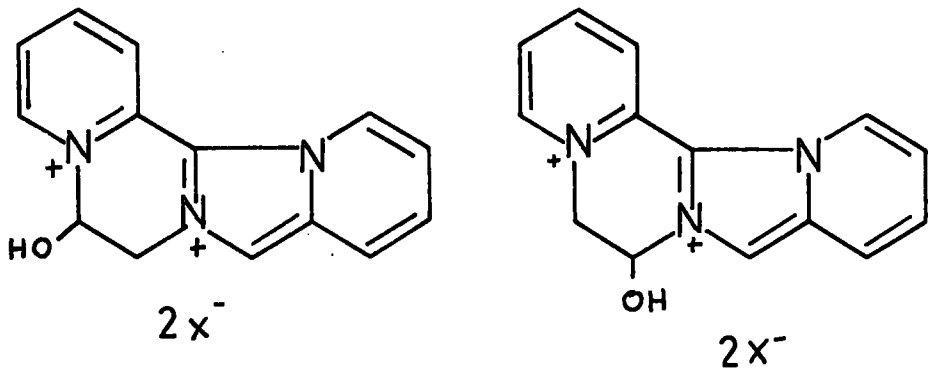
The infrared spectrum of the bromide salt (LXXXV; X = Br) showed no bands attributable to carbonyl or NH^+ absorption and the ultraviolet spectrum contained only a single broad band at 313mμ. The n.m.r. spectrum of this bromide in deuterium oxide showed a collection of protons in the region τ0.3 - 2.3 together with a triplet centred at τ3.0 and a doublet centred at τ4.5.

The position and nature of these last two signals were almost identical with the triplet and doublet which occur in the n.m.r. spectrum of the 6 - hydroxy - 6,7 - dihydropyrido [1,2-a; 2', 1'-c] pyrazidiinium cation (LXXXVI)[57] and attributed to the proton on the hydroxylated carbon atom and to the protons of the methylene group respectively.



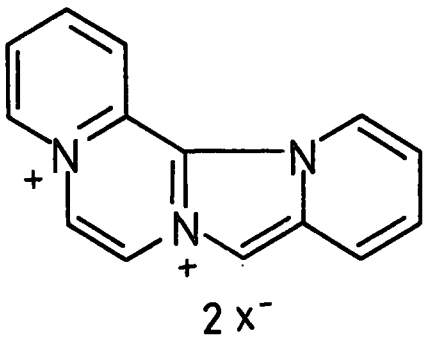
(LXXXVI)

The presence in the quaternary salt (LXXXV) of a monohydroxylated ethylene bridge between two quaternary nitrogen atoms was therefore indicated. Structures consistent with the spectroscopic and analytical data for the salts (LXXXV) are the hydroxy - 6,7 - dihydropyrido [1,2-a] imidazo [3,2-c] pyrazidiinium salts (LXXXV; X = Br, Cl or ClO_4).



(LXXXV)

The hydroxy dibromide (LXXXVI; X = Br) was dehydrated to the corresponding aromatic system by boiling under reflux with phosphorus tribromide[56]. Hence, attempts were made to dehydrate the quaternary salt of suggested structure (LXXXV; X = Br) by boiling under reflux with phosphorus tribromide; the starting material was recovered unchanged even after prolonged boiling. However, the salt (LXXXV; X = Cl) when boiled under reflux with thionyl chloride[58] lost the elements of water giving a diquaternary salt the analytical data for which and for the derived dipicrate were consistent with its being the aromatic system (LXXXVII; X = Cl).



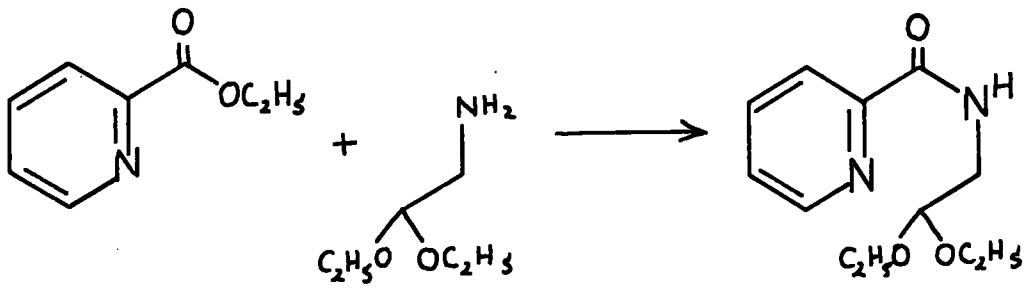
(LXXXVII)

The ultraviolet violet absorption spectrum of the dichloride (LXXXVII; X = Cl) showed a series of ten maxima, the longest wavelength maximum being at 412mμ. The infrared spectrum showed a new peak at 1675cm^{-1} also shown by the aromatic dipyrido [1,2-a; 2', 1'-c] pyrazidiinium salts (XLVII)[57]. The n.m.r. spectrum of the dichloride (LXXXVII; X = Cl) in deuterium oxide showed that the cation contained no protons with a τ value greater than 2.5.

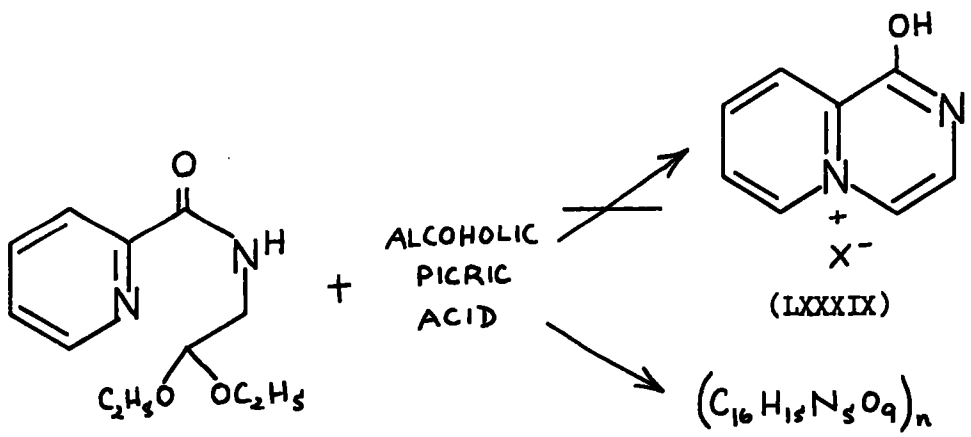
Further evidence for the suggested structure for these new systems is being sought together with an explanation as to their method of formation.

THE ACTION OF ALCOHOLIC PICRIC ACID ON N-(2,2- DIETHOXYETHYL) 2- PICOLINAMIDE (LXXXVIII).

With a view to the preparation of 1 - hydroxypyrido [1,2-a] pyrazinium salts, cyclisation of the amide (LXXXVIII) formed by the condensation between ethyl picolinate and aminoacetal was attempted by boiling it under reflux with alcoholic picric acid.



(LXXXVIII)



(LXXXIX)

$(C_{16}H_{15}N_5O_9)_n$

(XC)

Since the molecular formula of the picrate (XC) isolated did not correspond to the required 1 - hydroxy - salt (LXXXIX; X = picrate), this reaction sequence was not pursued further.

EXPERIMENTAL

All melting points were determined on a Kofler block.

Infrared absorption spectra were determined on a Perkin-Elmer 237 spectrometer, ultraviolet absorption spectra on a Unicam S.P. 500 spectrophotometer and n.m.r. spectra on a Perkin-Elmer Model R 10 spectrometer. The determination of ultraviolet spectra were carried out in aqueous solution unless otherwise stated.

Microanalyses were carried out by Drs. G. Weiler and F.B. Strauss.

ACETALDEHYDE - (2 - PYRIDYLMETHYLENEAMINO) DIETHYLACETAL (LVIII)

was prepared by the method of Hart[63]. Condensation of freshly distilled pyridine - 2 - aldehyde (9.32g.) with aminoacetal (11.46g.) gave the anil, b.p. 112°/1mm. (18.2g., 94%) (lit.,[63] b.p. 160°/11mm) (Found : C, 64.6; H, 8.5; N, 13.3. Calc. for $C_{12}H_{18}N_2O_2$: C, 64.8; H, 8.2; N, 12.6%); λ_{max} 237, 263sh., 268 and 273sh. mμ ($\log_{10}\epsilon$ 3.71, 353, 3.57 and 3.54).

ACETALDEHYDE - (METHYL - 2 - PYRIDYLMETHYLENEAMINO) DIETHYLACETAL (LXXVI)

was prepared by the method of Hart[63]. Condensation of 2 - acetylpyridine (20.6g.) with aminoacetal (22.6g.) gave the anil, b.p. 112°/0.3mm. (25.6g., 57%) (Found : C, 65.9; H, 8.7; N, 12.8. $C_{13}H_{20}N_2O_2$ requires C, 66.1; H, 8.5; N, 12.9%).

THE REACTION BETWEEN ACETALDEHYDE - (2 - PYRIDYLMETHYLENEAMINO) DIETHYLACETAL (LVIII) AND ALCOHOLIC PICRIC ACID.

A solution of the anil (LVIII) (4.11g.) in alcoholic picric acid (90ml.) was evaporated down to one third volume on a boiling water bath. The cooled solution was filtered and the picrate (LIX or LX; X = picrate) crystallised from ethanol giving yellow needles, m.p. 139-140° (3.96g., 74%) (Found : C, 53.4; H, 4.7; N, 16.6. $C_{26}H_{27}N_7O_9$ requires C, 53.7; H, 4.7; N, 16.9%).

The bromide was obtained by passing a methanolic solution of the above picrate through an Amberlite I.R.A. - 400 (Br) anion exchange resin. Evaporation of the eluate gave the bromide hemihydrate which crystallised from acetone as hygroscopic off white prisms, m.p. 144-146°

(Found : C, 54.6; H, 5.8; N, 12.6. $C_{20}H_{25}BrN_4O_2$. $\frac{1}{2}H_2O$ requires C, 54.3; H, 5.9; N, 12.7%); λ_{max} 211 and 318mμ ($\log_{10}\epsilon$ 4.45 and 4.10).

The perchlorate was obtained by passing a methanolic solution of the above picrate through an Amberlite I.R.A. - 400 (ClO_4) anion exchange resin. Evaporation of the eluate gave a gum, which when triturated with ether gave the perchlorate which crystallised from ethanol-ether as white prisms, m.p. 112-113° (Found : C, 52.7; H, 5.8; N, 11.7. $C_{20}H_{25}ClN_4O_6$ requires C, 53.0; H, 5.6; N, 12.4%).

THE ACTION OF CONCENTRATED MINERAL ACIDS ON ACETALDEHYDE (2- PYRIDYLMETHYLENEAMINO) DIETHYLACETAL (LVIII)

(a) A solution of the anil (LVIII) (2.0g.) in concentrated hydrochloric acid (10ml.) was boiled under reflux for 20 min. Addition of acetone to the cooled solution precipitated a crystalline solid, probably N,N - di- (2 - pyridylmethylene) pyrazidiinium dichloride (III; X = Cl) which crystallised from aqueous methanol as the dihydrate, m.p. >350° (0.44g., 27%) (Found; C, 52.4; H, 4.9; Cl, 18.6; N, 14.5; $C_{16}H_{14}Cl_2N_4$. $2H_2O$ requires C, 52.1; H, 4.9; Cl, 19.2; N, 15.2%); λ_{max} 217.5, 230, 235, 243sh., 278 and 288mμ ($\log_{10}\epsilon$ 3.98, 3.93, 3.93, 3.81, 4.30 and 4.37).

(b) Concentrated hydrochloric acid (15ml.) was slowly added, with stirring, to a mixture of pyridine - 2 - aldehyde (1.92g.) and aminoacetal (2.61g.) at -80°. The resulting solution was boiled under reflux for 20 min., cooled and the above dichloride which was precipitated by addition of acetone was crystallised from aqueous methanol (1.04g., 32%).

The dibromide was prepared by methods (a) and (b) by boiling the anil (LVIII) or a mixture of pyridine - 2 - aldehyde and aminoacetal under reflux with concentrated hydrobromic acid and precipitating the dibromide from the aqueous solution by addition of ethanol. Crystallisation from aqueous methanol gave the dibromide as off white prisms, m.p. $>350^{\circ}$. Yields of 20% and 23% were obtained using methods (a) and (b) respectively. (Found : C, 45.5; H, 3.6; Br, 37.7; N, 13.1. $C_{16}H_{14}Br_2N_4$ requires C, 45.5; H, 3.4; Br, 37.9; N, 13.2%).

Attempts to determine the molecular weight of the above salts by osmometry gave no satisfactory results.

The dipicrate which was obtained by addition of aqueous sodium picrate to the dichloride, crystallised from water as yellow plates, m.p. $>350^{\circ}$ (Found : C, 47.1; H, 2.5; N, 19.3. $C_{28}H_{18}N_{10}O_{14}$ requires C, 46.8; H, 2.5; N, 19.5%); λ_{max} 276, 288, 315 and 361mμ ($\log_{10}\epsilon$ 4.37, 4.41, 4.25 and 4.42).

The diperchlorate was obtained by : -

(a) the addition of 60% perchloric acid to an aqueous solution of the dichloride; the salt precipitated by the addition of ethanol crystallised from water as pale yellow plates, m.p. $>350^{\circ}$ (Found : C, 41.5; H, 3.3. $C_{16}H_{14}Cl_2N_4O_8$ requires C, 41.7; H, 3.1%).

(b) the action of 58% perchloric acid on the anil (LVIII) as described on p. 72.

THE ACTION OF CONCENTRATED MINERAL ACIDS ON ACETALDEHYDE - (METHYL - 2 - PYRIDYLMETHYLENEAMINO) DIETHYLACETAL (LXXVI)

The dichloride of molecular formula ($C_{18}H_{18}Cl_2N_4$) was obtained by either boiling the anil (LXXVI) or a mixture of 2 - acetylpyridine and aminoacetal under reflux with concentrated hydrochloric acid and precipitating the salt, probably N,N - di- (methyl - 2 - pyridylmethylene) pyrazidiinium dichloride (LXXVII; X = Cl), by the addition of ethanol. Crystallisation from aqueous methanol gave the dichloride dihydrate as pale green plates, m.p. >350°. Yields of 22% and 19% respectively, were obtained using the above reagents. (Found : C, 54.4; H, 5.5; Cl, 17.9; N, 13.5. $C_{18}H_{18}Cl_2N_4 \cdot 2H_2O$ requires C, 54.4; H, 5.6; Cl, 17.8; N, 14.1%).

The dibromide was obtained, similarly, by boiling a mixture of 2 - acetylpyridine (1.0g.) and aminoacetal (1.0g.) under reflux with concentrated hydrobromic acid and precipitating the salt from aqueous solution by the addition of ethanol. Crystallisation from aqueous ethanol gave the dibromide monohydrate as pale green plates, m.p. >350° (0.29g., 11%) (Found : C, 46.6; H, 4.3; Br, 34.3; N, 11.9. $C_{18}H_{18}Br_2N_4 \cdot H_2O$ requires C, 46.2; H, 4.3; Br, 34.1; N, 12.0%).

CATALYTIC REDUCTION OF THE SALT [(III; X = Cl,) PROBABLY N,N - DI - (2 - PYRIDYLMETHYLENE) PYRAZIDIINIUM DICHLORIDE].

A solution of the dichloride (III; X = Cl) (0.67g.) in methanol (25ml.) was hydrogenated to completion over Adam's catalyst at room temperature and pressure. The catalyst was filtered off, the solvent removed by evaporation under reduced pressure giving a salt of molecular formula

($C_{16}H_{22}Cl_2N_4$) probably N,N- di - [2 - (3,4,5,6 - tetrahydropyridyl) methylene] pyrazidiinium dichloride (LXII; X = Cl), which crystallised as colourless plates of the trihydrate from ethanol/di - isopropyl ether, m.p. >350° (0.45g., 63%) (Found: C, 48.6; H, 7.0; N, 14.6. $C_{16}H_{22}Cl_2N_4 \cdot 3H_2O$ requires C, 48.6; H, 7.1; N, 14.2%); λ_{max} 225mμ $\log_{10} \epsilon$ 3.95) in ethanol.

The dibromide (LXII; X = Br) was obtained, similarly, by the catalytic reduction of the dibromide (III; X = Br) (0.44g.). Crystallisation from ethanol/di - isopropyl ether gave the dibromide monohydrate as colourless plates, m.p. > 350° (0.28g., 60%) (Found: C, 42.9; H, 5.2; N, 11.9. $C_{16}H_{22}Br_2N_4 \cdot H_2O$ requires C, 42.9; H, 5.4; N, 12.4%).

Catalytic hydrogenation of both the dichloride and the dibromide (III; X = Cl or Br) at 70° and a pressure of 4 ats., gave the corresponding dichloride trihydrate and dibromide monohydrate (LXII; X = Cl or Br) respectively, in the above mentioned yields.

The dipicrate which was obtained by addition of aqueous sodium picrate to the dichloride, crystallised from water as yellow plates, m.p. 264-266° (Found: C, 46.5; H, 3.8; N, 19.2. $C_{28}H_{26}N_{10}O_{14}$ requires C, 46.3; H, 3.6; N, 19.3%).

CATALYTIC REDUCTION OF THE DICHLORIDE (LXXVII; X = Cl) TO GIVE A SALT (LXXVIX; X = Cl) OF MOLECULAR FORMULA ($C_{18}H_{26}Cl_2N_4$), PROBABLY N,N- DI - [METHYL - 2 - (3,4,5,6 - TETRAHYDROPYRIDYL) METHYLENE] PYRAZIDIINIUM DICHLORIDE.

A solution of the dichloride (LXXVII, X = Cl) (0.25g.) in aqueous methanol (20ml.) was hydrogenated to completion over Adam's catalyst at room temperature and pressure. The catalyst was filtered off and the solvent removed by evaporation under reduced pressure. The resulting dichloride (LXXVIX; X = Cl) crystallised as the trihydrate from aqueous acetone, m.p. >350° (0.2g., 72%) (Found : C, 50.8; H, 7.4; N, 12.9. $C_{18}H_{26}Cl_2N_4 . 3H_2O$ requires C, 51.1; H, 7.6; N, 13.2%).

The dipicrate which was obtained by addition of aqueous sodium picrate to the dichloride, crystallised from water as yellow needles, m.p. 273 - 275° (decomp.) (Found : C, 48.2; H, 4.1; N, 18.5. $C_{30}H_{30}N_{10}O_{14}$ requires C, 47.8; H, 4.0; N, 18.6%).

THE ACTION OF 58% PERCHLORIC ACID ON ACETALDEHYDE - (2 - PYRIDYLMETHYLENEAMINO) DIETHYLACETAL (LVIII)

A solution of the anil (LVIII) (3.0g.) in 58% perchloric acid (30ml.) was heated on a boiling water bath for 4 hr. and then cooled; the precipitated diperchlorate (III; X = ClO_4) was filtered and crystallised from water as pale yellow plates m.p. >350° (0.53g., 17.0%).

The filtrate was heated on a boiling water bath, for a further 20 hr. and cooled. The N,N- di - (2 - picolyl) - 2,5 - dioxoperhydropyrazine dihydroperchlorate (LXIV) which was precipitated by the addition of ethanol, crystallised from water as colourless plates, m.p. indefinite (0.38g., 23%)

(Found : C, 38.6; H, 3.9; N, 11.6. $C_{16}H_{16}N_4O_2 \cdot 2HClO_4$ requires C, 38.7; H, 3.7; N, 11.3%) λ_{max} 256.5sh., 260 and 266mμ ($\log_{10}\epsilon$ 3.78, 3.84 and 3.74).

The filtrate from the above dihydroperchlorate was evaporated to near dryness, cooled and the residue, probably the hydroxy - 6,7 - dihydropyrido [1,2-a] imidazo [3,2-c] pyrazidiinium diperchlorate (LXXXV; X = ClO_4) was filtered off. Crystallisation from water gave yellow prisms, m.p. 252-255° (decomp.) (1.07g., 18%). The analytical data for this compound is recorded on p. 87.

N,N - DI - (2 - PICOLYL) - 2,5 - DIOXOPERHYDROPYRAZINE (LXVI)

(a) An aqueous solution of the dihydroperchlorate (LXIV) (1.5g.) was basified with aqueous sodium hydroxide and extracted with chloroform. The extract was dried (Na_2SO_4), the solvent removed by evaporation under reduced pressure and the resulting dilactam purified by sublimation in vacuo, m.p. 147-148° (0.8g., 90%) (Found : C, 64.5; H, 5.3; N, 18.8. $C_{16}H_{16}N_4O_2$ requires C, 64.8; H, 5.4; N, 18.9%). λ_{max} 257, 262, and 269mμ ($\log_{10}\epsilon$ 3.80, 3.87 and 3.74).

(b) The dilactam was also obtained by passing an aqueous solution of the dihydrobromide (LXXIII) (0.73g.) through a Permutit de-acidite FF (SRA) 69 (OH) anion exchange resin. Evaporation of the eluate and sublimation of the resulting residue gave the dilactam, (0.45g., 95.3%).

The molecular weight of the dilactam as determined by ultraviolet spectrophotometric measurements on the dipicrate[72], by osmometry and from the mass spectrum of the free base gave values of 296, 289 and 296 respectively.

The dipicrate, obtained by addition of alcoholic picric acid to the dilactam, crystallised from nitromethane as yellow prisms, m.p. 252-254° (Found : C, 44.3; H, 3.1; N, 18.8 $C_{16}H_{16}N_4O_2 \cdot 2C_6H_3N_3O_7$ requires C, 44.6; H, 2.9; N, 18.6%).

ATTEMPTED SYNTHESIS OF 2 - PYRIDYL - Δ^2 - OXAZOLINE (LXVII)

Attempts to synthesise 2 - pyridyl - Δ^2 - oxazoline by the methods of Boyd and Hansen[69] and Boyd and Rittner[70] were unsuccessful. The only identifiable product isolated was 1- oxo - 1,2,3,4 - tetrahydropyrido [1,2-a] pyrazinium chloride (LXIX; X = Cl).

N - 2 - HYDROXYETHYLBENZAMIDE

A suspension of ethanolamine (3g.) in 30% sodium hydroxide solution (20ml.) was treated with benzoyl chloride (7g.), a violent reaction occuring. The mixture was cooled and extracted with chloroform. The organic layer was washed with dilute hydrochloric acid, dried (Na_2SO_4) and the solvent removed by evaporation under reduced pressure giving a colourless oil. Trituration of this oil with petroleum ether b.p. 40-60° gave the amide as a white solid, m.p. 59-61° (lit.,[70] m.p. 62.5-63.5°) (5.3g., 65%).

2 - PHENYL - Δ^2 - OXAZOLINE

was prepared by the method of Wenker[76]. Treatment of the above amide (6.15g.) with phosphorus pentoxide (6.15g.) gave the oxazoline which was purified by distillation in vacuo, b.p. 70-77°/1mm. (Bath temp.) (lit., b.p. 99-100°/2mm.,[70] 242-243°[76]) (1.65g., 30%).

The picrate obtained by addition of alcoholic picric acid to the oxazoline and crystallised from ethanol as yellow prisms, m.p. 180-182° (lit., m.p. 179-180°[70], 177°[76]).

PERHYDRO - N,N- DI - (2 - PICOLYL) 2,5 - DIOXOPYRAZINE (LXX)

A solution of the dilactam (LXVI) (0.26g.) in glacial acetic acid (25ml.) was hydrogenated to completion over Adam's catalyst at atmospheric temperature and pressure. The catalyst was filtered off, the solvent evaporated under reduced pressure and the residue made alkaline with aqueous sodium hydroxide. The dried (Na_2SO_4) ethereal extract of the alkaline solution was evaporated to dryness giving the dilactam which crystallised from isopropanol/di - isopropyl ether, m.p. 150-152° (0.14g., 52%) (Found: C, 62.5; H, 9.1; N, 18.0. $C_{16}H_{28}N_4O_2$ requires C, 62.3; H, 9.2; N, 18.2%).

The dipicrate obtained by addition of alcoholic picric acid to the dilactam, crystallised from water as yellow prisms, m.p. 291-294° (Found: C, 43.7; H, 4.5. $C_{16}H_{28}N_4O_2 \cdot 2C_6H_3N_3O_7$ requires C, 43.9; H, 4.5%).

THE ACTION OF SODIUM BOROHYDRIDE ON THE REDUCTION PRODUCT (LXII), PROBABLY N,N-DI-[2-(3,4,5,6-TETRAHYDROPYRIDYL) METHYLENE] PYRAZIDIINIUM DIHALIDE.

An unsuccessful attempt was made to reduce the dichloride (LXII; X = Cl) with sodium borohydride in aqueous methanol; no identifiable material was obtained.

PERHYDRO - N,N- DI -(2 - PICOLYL) PYRAZINE (IV)

(a) A solution of the base (LXXI) (0.48g.) in glacial acetic acid (25ml.) was hydrogenated to completion over Adam's catalyst at atmospheric temperature and pressure. The catalyst was filtered off, the solvent

evaporated under reduced pressure and the residue basified with aqueous sodium hydroxide. The dried (Na_2SO_4) ethereal extract of the alkaline solution was evaporated to dryness and the resulting perhydro base was purified by sublimation in vacuo, m.p. 119-121° (0.35g., 70%) (Found : C, 68.7; H, 11.4; N, 19.6. $C_{16}H_{32}N_4$ requires C, 68.5; H, 11.5; N, 20.0%).

(b) A suspension of the dilactam (LXX) (0.53g.) in dry ether (60ml.) was slowly added to a stirred solution of lithium aluminium hydride (1.35g.) in dry ether (40ml) and the resulting mixture boiled under reflux for 4 days, cooled and the excess hydride decomposed with water. An ethereal extract of the alkaline solution was dried (Na_2SO_4) and the solvent evaporated. The resulting gummy residue was washed with the minimum of ether and then sublimed in vacuo giving the perhydro base, (0.32g., 66%).

The tetrapicrate obtained by addition of alcoholic picric acid to the perhydro base, crystallised from water as yellow plates, m.p. 249-251° (Found : C, 40.5; H, 4.1. $C_{16}H_{32}N_4 \cdot 4C_6H_3N_3O_7$ requires C, 40.1; H, 3.7%).

The tetrahydrochloride was obtained by warming a solution of the perhydro base in the minimum of concentrated hydrochloric acid for 5 min. The solution was cooled and the salt precipitated by the addition of acetone, crystallised from methanol-acetone, m.p. 335-338° (decomp.) (Found : C, 44.4; H, 8.2; N, 13.0. $C_{16}H_{32}N_4 \cdot 4HCl$ requires C, 45.1; H, 8.5; N, 13.1%).

N,N- DI- (2- PICOLYL) PERHYDROPYRAZINE (LXXI)

(a) Sodium borohydride (0.51g.) was slowly added to a stirred solution of the dichloride (III; X = Cl) in methanol (10ml.) and water (1ml.). The mixture was boiled under reflux for 10 min., cooled and the excess hydride decomposed with water. The ethereal extract of the aqueous

solution was dried (Na_2SO_4) and the solvent removed by evaporation. The resulting base was purified by sublimation in vacuo, m.p. 93-95° (0.35g., 94%) (Found : C, 72.0; H, 7.5; N, 20.6. $C_{16}H_{20}N_4$ requires C, 71.6; H, 7.5; N, 20.9%); λ_{max} 200, 257sh., 262 and 268mμ ($\log_{10}\epsilon$ 4.08, 3.76, 3.82 and 3.41).

(b) A solution of the dilactam (LXVI) (0.61g.) in dry ether (30ml.) was slowly added to a stirred solution of lithium aluminium hydride (0.8g.) in dry ether (20ml.) and the resulting suspension was boiled under reflux for 4 hr; cooled and the excess hydride decomposed with water. The ethereal extract of the aqueous solution was dried (Na_2SO_4), the solvent removed by evaporation and the resulting base purified by sublimation in vacuo, (0.46g., 83%).

The molecular weight of the base as determined by ultraviolet spectrophotometric measurements on the tetrapicrate[72] and from the mass spectrum of the free base was 268.

The tetrapicrate obtained by addition of alcoholic picric acid to the base, crystallised from water as yellow plates, m.p. 228-230° (Found : C, 40.7; H, 2.9. $C_{16}H_{20}N_4 \cdot 4C_6H_3N_3O_7$ requires C, 40.6; H, 2.7%).

The dimethiodide was obtained by boiling under reflux a dry ethereal solution of the base with methyl iodide. The dimethiodide was filtered and crystallised from methanol, m.p. 205-206° (Found : C, 39.0; H, 5.0; N, 9.9. $C_{18}H_{26}I_2N_4$ requires C, 39.1; H, 4.7; N, 10.2%).

N,N- DI - (METHYL - 2 - PICOLYL) PERHYDROPYRAZINE (LXXVIII)

Sodium borohydride (1.21g.) was slowly added to a stirred solution of the dichloride (LXXVII; X = Cl) (1.17g.) in methanol (10ml.) and water(1ml.). The mixture was boiled under reflux for 10 mins., cooled and the excess hydride decomposed with water. The ethereal extract of the aqueous solution was dried (Na_2SO_4) and the solvent removed by evaporation. The residual gum was washed with the minimum of ether and the resulting base was purified by sublimation, m.p. 103-105° (0.53g., 61%) (Found : C, 73.1; H, 8.0; N, 18.6; $C_{18}H_{24}N_4$ requires C, 72.9; H, 8.2; N, 18.9%).

The dipicrate obtained by addition of alcoholic picric acid to the base, crystallised from water as yellow plates, m.p. 229-231° (Found : C, 47.6; H, 3.9. $C_{18}H_{24}N_4 . 2C_6H_3N_3O_7$ requires C, 47.8; H, 4.0%).

ETHYL PICOLINATE

A solution of picolinic acid (50g.) in dry ethanol (150ml.) and concentrated sulphuric acid (60ml.) was boiled under reflux for 4 hr.; cooled, concentrated sulphuric acid (40ml.) added and the resulting solution boiled under reflux for a further 15 min. The cooled solution was poured onto crushed ice (500g.), sodium bicarbonate (62.5g.) added and the solution basified by addition of concentrated ammonium hydroxide (160ml.). The ethereal extract of the alkaline solution was dried (Na_2SO_4), the solvent removed by evaporation and the resulting ester was distilled in vacuo, b.p. 79°/13mm. (lit.,[77] b.p. 125-127°/14mm.) (52.1g., 71%).

N - (2 - HYDROXYETHYL) - 2 - PICOLINAMIDE (LXVIII)

Ethyl picolinate (11g.) and ethanolamine (4.7g.) were heated together in a sealed tube at 160° for 12 hr., cooled and the resulting hydroxyamide was distilled in vacuo, b.p. 167°/1.6mm. (10.6g., 88%) (Found C, 57.4; H, 6.1. $C_8H_{10}N_2O_2$ requires C, 57.8; H, 6.1%); λ_{max} 218, 223sh. and 265.5mμ ($\log_{10}\epsilon$ 3.93, 3.89 and 3.71).

The monopicrate obtained by addition of alcoholic picric acid to the hydroxyamide, crystallised from ethanol as yellow plates, m.p. 159.5-160.5° (Found : C, 42.8; H, 3.7. $C_8H_{10}N_2O_2 \cdot C_6H_3N_3O_7$ requires C, 42.5; H, 3.3%)

1- OXO - 1,2,3,4 - TETRAHYDROPYRIDO [1,2-a] PYRAZINIUM BROMIDE (LXIX; X = Br)

A solution of phosphorus tribromide (2.5g.) in dry benzene (80ml.) was added to the above hydroxyamide (3.1g.) in dry benzene (20ml.). A white solid separated and this suspension was boiled under reflux for 12 hr., cooled and the benzene decanted. The residue was washed with ethanol and crystallised from aqueous ethanol giving the quaternary bromide m.p. >350° (1.43g., 42%) (Found : C, 41.7, H, 4.0; N, 12.0. $C_8H_9BrN_2O$ requires C, 42.0; H, 4.0; N, 12.2%).

The monopicrate obtained by addition of aqueous sodium picrate to the bromide, crystallised from water as yellow needles, m.p. 184-186° (Found : C, 44.9; H, 2.5; N, 19.2. $C_{14}H_{11}N_5O_8$ requires C, 44.6; H, 2.9; N, 18.6%)

1- OXOPERHYDROPYRIDO [1,2-a] PYRAZINE. HYDROBROMIDE

A solution of the above bromide (1.01g.) in methanol (25ml.) was hydrogenated to completion over Adam's catalyst at room temperature and pressure. The catalyst was filtered off and the solvent removed by evaporation under reduced pressure.

The resulting hydrobromide crystallised from aqueous ethanol, m.p. >350° (0.91g., 88%) (Found : C, 41.1; H, 6.4. $C_8H_{14}N_2O$. HBr requires C, 40.9; H, 6.4%).

1- OXOPERHYDROPYRIDO [1,2-a] PYRAZINE (LXXII)

An aqueous solution of the above hydrobromide (0.5g.) was basified with aqueous sodium hydroxide. The ethereal extract of the alkaline solution was dried (Na_2SO_4) and the solvent removed by evaporation. The resulting lactam crystallised from aqueous acetone as white needles, m.p. 136-137° (lit.,[73] m.p. 134-134.5°) (0.30g., 91%).

Alternatively, the lactam was purified by sublimation in vacuo.

PERHYDROPYRIDO [1,2-a] PYRAZINE (II)

A solution of the above lactam (0.97g.) in dry ether (30ml.) was slowly added to a stirred suspension of lithium aluminium hydride (2.07g.) in dry ether (20ml.) and the resulting suspension boiled under reflux for 3 hr., cooled and the excess hydride decomposed by the addition of water. The ether layer was decanted and the residue ether extracted; the combined ethereal layers were dried (Na_2SO_4), the solvent removed by evaporation and the resulting perhydro base distilled in vacuo, b.p. 95-103°/25mm. (bath temp.) (0.69g., 78%) (lit.,[73] b.p. 98-99°/25mm.)

The dipicrate obtained by addition of alcoholic picric acid to the perhydro base, crystallised from water as yellow needles, m.p. 275-278° (decomp.) [lit., m.p. 240°[74], 250-260°[75] (decomp.)] (Found : C, 40.1; H, 3.6; N, 19.0. Calc. for $C_8H_{16}N_2 \cdot 2C_6H_3N_3O_7$: C, 40.1; H, 3.7; N, 18.7%).

The dihydrochloride was prepared by passing dry hydrogen chloride through a dry ethereal solution of the perhydro base. The precipitated dihydrochloride was filtered off and crystallised from isopropanol, m.p. 209-211° (lit.,[74] m.p. 210-212°).

THE ACTION OF ALKALI ON THE DICHLORIDE [III; X = Cl, PROBABLY N,N- DI - (2 - PYRIDYLMETHYLENE) PYRAZIDIINIUM DICHLORIDE].

(a) A solution of the dichloride (III; X = Cl) (0.58g.) in water (10ml.) was treated with 30% sodium hydroxide solution until precipitation of the red solid ceased. Addition of concentrated hydrochloric acid (4ml.) to a suspension of this red solid in water (3ml.) gave a precipitate which was filtered off. Crystallisation from aqueous ethanol gave the original dichloride (0.29g., 50%).

A similar series of reactions occured with the methyl derivative (LXXVII; X = Cl) of the above dichloride.

(b) A solution of the dichloride (III; X = Cl) (0.82g.) in the minimum of water was treated with aqueous sodium hydroxide until precipitation of the red solid ceased. The precipitate was filtered, dissolved in water (50ml.) and the resulting solution boiled under reflux for 30 min. Evaporation of this solution to dryness, under reduced pressure, gave a red gum. Treatment of this gum with ethanolic hydrochloric acid (10ml.) gave a precipitate (sodium chloride) which was removed by filtration. The filtrate, on evaporation to dryness gave a brown solid, which when boiled with ethanol (10ml.) for 5 min. gave the dihydrochloride of the dilactam (LXVI) which crystallised from aqueous ethanol as colourless plates, m.p. indefinite (0.66g., 81%)

(Found : C, 51.7; H, 4.9; N, 14.8. $C_{16}H_{16}N_4O_2$. 2HCl requires C, 52.1; H, 4.9; N, 15.2%).

(c) Passage of an aqueous solution of the dichloride (III; X = Cl) through an Amberlite I.R.A. - 400 (OH) anion exchange resin and evaporation of the eluate to dryness gave a red gum as obtained in method (b) but free from inorganic material. Subsequent treatment of this gum as described in method (b) gave the dihydrochloride of the dilactam (LXVI) in 81% yield.

(d) The dilactam dihydrobromide (LXXIII) was obtained by treating the red gum, as obtained in method (c) from the dichloride (III; X = Cl) (1.01g.), with ethanolic hydrobromic acid (10ml.). This solution was evaporated to dryness and the resulting solid boiled with ethanol (10ml.). The dihydrobromide was filtered and crystallised from aqueous ethanol as colourless plates, m.p. indefinite (0.84g., 77%) (Found : C, 42.0; H, 4.0; N, 12.0. $C_{16}H_{16}N_4O_2$. 2HBr requires C, 42.0; H, 4.0; N, 12.2%).

Preparation of the dilactam dihydrobromide (LXXIII) as prescribed by method (b) gave a yield of 57% based on the starting dichloride (III; X = Cl).

THE ACTION OF ALKALI ON THE SALT [LXXVII; X = Cl, PROBABLY N,N- DI - (METHYL - 2 - PYRIDYLMETHYLENE) PYRAZIDIINIUM DICHLORIDE].

(a) An aqueous solution of the dichloride (LXXVII; X = Cl) (1.05g./25ml.) was passed through an Amberlite I.R.A. - 400 (OH) anion exchange resin and the eluate evaporated to dryness under reduced pressure. The residual red gum was dissolved in concentrated hydrochloric acid (5ml.)

and the resulting solution heated on a water bath for 5 min., cooled and the dihydrochloride precipitated by addition of acetone. Crystallisation from ethanol-ether gave the dihydrochloride as white prisms, m.p. indefinite (0.96g., 86%) (Found : C, 51.1; H, 5.9; N, 13.2. $C_{18}H_{20}N_4O_2$. 2HCl. $1\frac{1}{2}H_2O$ requires C, 51.0; H, 5.9; N, 13.2%).

(b) The corresponding dihydrobromide was prepared by treating the red gum obtained in method (a) with concentrated hydrobromic acid. Addition of acetone to this solution precipitated the salt which crystallised from ethanol as colourless needles, m.p. indefinite (Found : C, 42.4; H, 5.0. $C_{18}H_{20}N_4O_2$. 2HBr. $1\frac{1}{2}H_2O$ requires C, 42.1; H, 4.9%).

THE BASE OF MOLECULAR FORMULA $C_{18}H_{16}N_4O_2$.

(a) The red gum, obtained from the dichloride (0.8g.) as described in the above method (a), was dissolved in alcohol (12ml.). Addition of ether (60ml.) precipitated a base which crystallised from ethanol/di-isopropyl ether as buff prisms, m.p. 259-261° (0.28g., 33%) (Found : C, 60.8, 60.9; H, 5.8, 5.8; N, 16.0, 15.8. $C_{18}H_{16}N_4O_2$. $2H_2O$ requires C, 60.7; H, 5.7; N, 15.7%).

(b) An aqueous solution of the dihydrochloride (0.96g.) of molecular formula $C_{18}H_{20}N_4O_2$. 2HCl. $1\frac{1}{2}H_2O$ was passed through an Amberlite I.R.A. - 4B(OH) anion exchange resin. The eluate was evaporated to dryness and the resulting base which crystallised from ethanol/di-isopropyl ether was identical with that obtained by method (a), (0.57g., 66%).

The dipicrate obtained by addition of alcoholic picric acid to the above base, crystallised from nitromethane - ether as yellow prisms, m.p. 164-165° (Found : C, 46.3; H, 3.1; N, 18.3. $C_{18}H_{16}N_4O_2 \cdot 2C_6H_3N_3O_7$ requires C, 46.3; H, 2.9; N, 18.0%).

N,N- DI- (METHYL - 2 - PICOLYL) 2,5- DIOXOPERHYDROPYRAZINE (LXXXII)

An aqueous solution of the dihydrochloride (LXXXI) (1.3g.) was basified with aqueous sodium hydroxide. The ethereal extract of the alkaline solution was dried (Na_2SO_4) and the ether removed by evaporation giving the base (0.03g.). The amount of material obtained prevented purification.

The dipicrate obtained by the addition of alcoholic picric acid to the base, crystallised from nitromethane as yellow prisms, m.p. 225-227° (Found : C, 45.9; H, 3.5; N, 18.0. $C_{18}H_{20}N_4O_2 \cdot 2C_6H_3N_3O_7$ requires C, 46.0; H, 3.4; N, 17.9%).

2- (1,3- DIOXOLAN - 2 - YL) PYRIDINE

was prepared according to the method of Bradsher and Parham[47]. Reaction between pyridine - 2 - aldehyde (21.4g.) and p-toluene sulphonic acid (10g.) in ethylene glycol (24ml.) gave 2- (1,3- dioxolan - 2 - yl) pyridine. b.p. 95°/2.2mm (lit.,[47] b.p. 122°/4mm) (22.1g., 73%) (lit.,[47] yield 71%).

2- BROMOETHYLAMINE HYDROBROMIDE

was prepared according to the method of Cortese[78]. Reaction of ethanolamine (10g.) with concentrated hydrobromic acid (99.4g.) gave 2- bromoethylamine hydrobromide, (22.3g., 68%).

REACTION BETWEEN 2- (1,3- DIOXOLAN - 2 - YL) PYRIDINE AND 2- BROMOETHYLAMINE HYDROBROMIDE

A mixture of 2- (1,3- dioxolan - 2 - yl) pyridine (0.37g.) and 2- bromoethylamine hydrobromide (0.31g.) was allowed to stand in tetramethylene sulphone for 5 days. The resulting solution was heated on a water bath for 2 hr., cooled and a brown gum was precipitated by the addition of ethyl acetate. This gum was heated with concentrated hydrobromic acid, cooled and a dibromide of molecular formula $C_{14}H_{15}Br_2N_3O$ (0.05g.) was precipitated by the addition of acetone. It was subsequently found that this same compound could be obtained in much higher yield using the method given below.

REACTION BETWEEN PYRIDINE - 2 - ALDEHYDE AND 2- BROMOETHYLAMINE HYDROBROMIDE

(a) A solution of 2- bromoethylamine hydrobromide (1.05g.) and pyridine - 2 - aldehyde (0.66g.) in concentrated hydrobromic acid (4ml.) was boiled under reflux for 15 min. and then cooled. The dibromide (LXXXIV) precipitated by addition of acetone, crystallised from methanol-ether as yellow plates, m.p. $>350^{\circ}$ (decomp.) (0.89g., 36%) (Found : C, 42.2%; H, 3.9; N, 10.3. $C_{14}H_{15}Br_2N_3O$ requires C, 41.9; H, 3.8; N, 10.5%); λ_{max} 201, 247, 251, 310 and 409mμ ($\log_{10}\epsilon$ 4.56, 3.99, 3.98, 3.59 and 4.39).

(b) The above dibromide was also prepared, in the same yield, by boiling a methanolic solution of pyridine - 2 - aldehyde and 2-bromoethylamine hydrobromide under reflux, followed by addition of ether to the cooled solution.

The dipicrate obtained by addition of aqueous sodium picrate to the dibromide, crystallised from water as yellow plates, m.p. 240-241° (Found : C, 46.0; H, 2.7; N, 19.3. $C_{26}H_{17}N_9O_{14}$ requires C, 46.0; H, 2.5; N, 18.6%).

The diperchlorate was obtained by addition of 60% perchloric acid to a solution of the dibromide. The salt preciptated by the addition of ethanol crystallised from aqueous ethanol, m.p. 301-303° (Found : C, 39.9; H, 3.0; N, 10.2. $C_{14}H_{13}Cl_2N_3O_8$ requires C, 39.8; H, 3.1; N, 10.0%).

As yet, a satisfactory structure has not been established for these salts.

CATALYTIC REDUCTION OF THE ABOVE DIBROMIDE GIVING A COMPOUND OF MOLECULAR FORMULA $C_{14}H_{21}N_3O_6$.

A solution of the above dibromide (1.21g.) in glacial acetic acid (25ml.) and water (3ml.) was hydrogenated to completion over Adam's catalyst. The catalyst was filtered off, the solvent evaporated and the residue made alkaline with aqueous sodium hydroxide. A chloroform extract of the alkaline solution was dried (Na_2SO_4), the solvent evaporated and the residual oil triturated with petroleum ether b.p. 40-60° giving a colourless solid which crystallised from acetone-ether, m.p. 134-136° (0.91g., 92%) (Found : C, 51.5, 51.0; H, 6.4, 6.6; N, 13.3, 12.9. $C_{14}H_{21}N_3O_6$ requires C, 51.4; H, 6.5; N, 12.8%).

The picrate obtained by addition of alcoholic picric acid to the above base, crystallised from ethanol as yellow needles, m.p. 107-110° (Found : C, 45.8; H, 4.8; N, 17.8%).

As yet, a satisfactory structure has not been established for the above base.

THE REACTION BETWEEN CONCENTRATED MINERAL ACIDS AND THE SALTS OF MOLECULAR FORMULA ($C_{20}H_{25}XN_4O_2$) (LIX or LX; X = Br or Cl).

A solution of the bromide (LIX or LX; X = Br) (1.1g.) in concentrated hydrobromic acid (10ml.) was boiled under reflux for 10 min., cooled and a salt of molecular formula $C_{14}H_{13}Br_2N_3O$ probably the hydroxy-6,7- dihydropyrido [1,2-a] imidazo [3,2-c] pyrazidiinium dibromide (LXXXV; X = Br) precipitated by addition of ethanol. Crystallisation from methanol/di-isopropyl ether gave yellow needles, m.p. 273-275° (decomp.) (1.0g., 51%) (Found : C, 42.4; H, 3.4; N, 10.5. $C_{14}H_{13}Br_2N_3O$ requires C, 42.1; H, 3.3; N, 10.6%); λ_{max} 314mμ ($\log_{10}\epsilon$ 4.06).

The diperchlorate was obtained by boiling under reflux for 3 min. a solution of the bromide (LIX or LX; X = Br) (0.5g.) in 58% perchloric acid (10ml.). The solution was cooled and the diperchlorate precipitated by addition of ethanol. Crystallisation from water gave the monohydrate, m.p. 253-255° (decomp.) (0.54g., 53%). (Found : C, 36.9; H, 3.4; N, 9.2. $C_{14}H_{13}Cl_2N_3O_9 \cdot H_2O$ requires C, 36.8; H, 3.3; N, 9.2%).

The diperchlorate was also prepared by the method described on p. 73.

The dichloride was obtained by boiling under reflux for 20 min. a solution of the chloride (LIX or LX; X = Cl) (0.62g.) in concentrated hydrochloric acid (10ml.). The solution was cooled and the salt precipitated by addition of ethanol-ether crystallised from methanol/ di-isopropyl ether, m.p. 210-212° (decomp.) (0.31g., 58%) (Found : C, 54.5; H, 4.3. $C_{14}H_{13}Cl_2N_3O$ requires C, 54.2; H, 4.2%).

ATTEMPTED PREPARATION OF PYRIDO [1,2-a] IMIDAZO [3,2-c] PYRAZIDIINIUM DIBROMIDE (LXXXVII; X = Br).

An unsuccessful attempt was made to dehydrate the above hydroxy compound (LXXXV; X = Br) using phosphorus tribromide[47]. Only the starting material was isolated.

PYRIDO [1,2-a] IMIDAZO [3,2-c] PYRAZIDIINIUM DICHLORIDE (LXXXVII; X = Cl)

A suspension of the hydroxy-dichloride (LXXXV; X = Cl) (0.48g.) in thionylchloride[58] (15ml.) was boiled under reflux for 20 hr. The reaction mixture was cooled and filtered giving the dichloride dihydrate which crystallised from methanol-ether, m.p. $>350^{\circ}$ (0.40g., 79%) (Found : C, 50.8; H, 4.6; N, 13.1. $C_{14}H_{11}Cl_2N_3 . 2H_2O$ requires C, 51.2; H, 4.6; N, 12.8%); λ_{max} 206sh., 243, 268, 272, 294, 306, 337sh., 353sh., 367 and 412mμ ($\log_{10}\epsilon$ 4.20, 4.36, 4.25, 4.25, 4.20, 4.31, 3.57, 3.79, 3.93 and 4.21).

The dipicrate obtained by addition of aqueous sodium picrate to the dichloride crystallised from water as yellow prisms, m.p. 255-256° (Found : C, 46.2; H, 2.2; N, 19.3. $C_{26}H_{15}N_9O_{14}$ requires C, 46.1; H, 2.2; N, 18.6%).

ATTEMPTED PREPARATION OF N- (2,2- DIETHOXYETHYL) - 2 - PICOLINAMIDE (LXXXVIII)

(a) A suspension of picolinic acid (1.27g.) in aminoacetal (1.35g.) was boiled under reflux for 15 min., cooled and a solid, 2,2-diethoxyethylammonium picolinate, was filtered and crystallised from benzene, m.p. 118-120° (1.68g., 63%) (Found : C, 56.6; H, 7.8, N, 11.6. $C_{12}H_{20}N_2O_4$ requires C, 56.2; H, 7.9; N, 10.9%).

(b) Picolinic acid (3.59g.) and aminoacetal (4.11g.) were heated together in a sealed tube at 150° for 12 hr. and then cooled to -40°. On opening the tube there was a violent release of pressure. The contents of the tube were distilled under reduced pressure giving the following fractions : -

(i) pyridine, b.p. 40°/0.6mm. (2.4g.),

(ii) the above picolinate, b.p. 95°/0.6mm. (1.7g.),

(iii) a very small amount of colourless liquid,

b.p. 150°/0.6mm., the infrared spectrum of which was identical with N- (2,2- diethoxyethyl) 2- picolinamide, the preparation of which is described below.

N- (2,2- DIETHOXYETHYL) 2- PICOLINAMIDE (LXXXVIII)

A mixture of ethyl picolinate (4.6g.) and aminoacetal (3.99g.) was heated in a sealed tube at 150° for 12 hr., cooled and the resulting picolinamide distilled in vacuo giving a colourless liquid, b.p. 141°/0.5mm. (3.45g., 48%) (Found : C, 60.5; H, 7.6; N, 11.7. $C_{12}H_{18}N_2O_3$ requires C, 60.5; H, 7.6; N, 11.7%); λ_{max} 219 and 266mμ ($\log_{10}\epsilon$ 3.93 and 3.72).

THE REACTION BETWEEN N- (2,2- DIETHOXYETHYL) 2- PICOLINAMIDE (LXXXVIII) AND ALCOHOLIC PICRIC ACID.

A solution of the substituted picolinamide (1.01g.) in alcoholic picric acid (25ml.) was boiled under reflux for 6 hr., the solution cooled and the picrate (XC) precipitated by the addition of ether. The picrate crystallised from ethanol as yellow needles, m.p. 141-142° (0.33g., 19%) (Found : C, 45.9; H, 3.5; N, 17.0. $C_{16}H_{15}N_5O_9$ requires C, 45.6; H, 3.6; N, 16.6%).

As yet a satisfactory structure for the above picrate has not been established.

1- METHYL - 3 - PHENYLPYRIDO [1,2-a] PYRAZINIUM BROMIDE

was prepared using the method described by Krohnke[36].

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